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CLINICAL PROFILES, PHARMACOTHERAPIES AND PROGNOSIS IN ACUTE HEART FAILURE

FOCUS ON VASOACTIVE MEDICATIONS

Tuukka Tarvasmäki

ACADEMIC DISSERTATION

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ABSTRACT

Acute heart failure (AHF), one of the most common reasons for hospitalizations, is associated with high mortality. Its management is challenging and should be tailored according to different clinical manifestations that range from less severe hypertensive AHF to the most severe form, cardiogenic shock (CS), with its extremely poor prognosis. Acute coronary syndrome (ACS) precipitates over one-third of AHF (ACS-AHF) cases.

The aim of this thesis is to analyze current real-life AHF management, with emphasis on vasoactive therapies, in relation to different AHF clinical presentations and specifically CS. In addition, the study targets for characterization two poorly described clinical pictures: 1) ACS-AHF and 2) CS complicated by acute kidney injury (AKI), a common organ injury in the critically ill.

Data from two independent prospectively collected patient cohorts in this thesis comprise the FINN-AKVA (Finnish Acute Heart Failure) study, which is a national multicenter study including 620 patients hospitalized for AHF, and the European multicenter CardShock study including 219 patients with CS.

Furosemide was the most common therapy for AHF regardless of clinical presentation, often administered even during the initial CS phase. Other intravenous medications and non-invasive ventilation varied according to the AHF clinical picture of AHF. Systolic blood pressure (SBP) was one of the main predictors of AHF-therapy utilization. Considering previous and current European guideline recommendations, use of nitrates was rather low, especially in hypertensive AHF.

Compared with AHF patients without concomitant ACS (nACS-AHF), ACS-AHF manifested as a more severe clinical presentation and more frequently as *de novo* AHF. Guideline-recommended AHF therapies and invasive coronary procedures were more frequent in ACS-AHF. However, angiography (35%) and revascularization (percutaneous coronary intervention 16% and coronary artery bypass graft surgery 10%) rates were low. ACS-AHF was associated with higher 30-day mortality than was AHF without concomitant ACS (13% vs 8%).

Use of vasopressors and inotropes was rather frequent in patients without shock, especially in pulmonary edema, and in ACS-AHF as well. They were used almost invariably in CS, noradrenaline being the most common vasopressor and dobutamine the inotrope of choice. Adrenaline was associated not only with excessive cardiac but also with 90-day mortality. In turn, noradrenaline combined with either dobutamine or levosimendan was associated with a more positive prognosis; these two combinations appeared to be alternatives with equivalent outcomes.

Patients with CS frequently developed AKI during their first 48 hours of shock, but incidence varied by definition. The AKI definition based on urine output (UO) seemed rather liberal compared with one based on creatinine or on cystatin C (CysC). In addition, creatinine- and CysC-defined AKIs were independently related to higher 90-day mortality, whereas the UO-based AKI definition was not. A stricter cutoff of <0.3 mL/kg/h for average UO during a 6-hour period was more accurate in mortality prediction. AKI was correlated with findings of arterial hypotension, low cardiac output, and venous congestion.

In conclusion, use of AHF pharmacotherapies turned out to be related to clinical class, SBP on admission, and ACS as the AHF precipitating factor. Nitrate use seemed rather low, whereas vasopressors and inotropes seem to have been overused. Adrenaline was associated with excessive cardiac injury and mortality. In AHF, concomitant ACS seemed to increase short-term mortality, whereas in CS, AKI was associated with increased mortality.

TIIVISTELMÄ

Äkillinen eli akuutti sydämen vajaatoiminta (ASV) on yksi yleisimmistä sairaalahoitoon johtavista sairauksista ja siihen liittyy huomattavan korkea kuolleisuus. ASV.n hoito on haastavaa johtuen epäyhtenäisestä taudinkuvasta, joka ulottuu korkean verenpaineen aiheuttamasta ASV:sta erittäin huonoennusteiseen sydänperäiseen sokkiin. Ainakin kolmasosassa tapauksista ASV:n taustalla on sepelvaltimotautikohtaus.

Väitöskirjan tavoitteena on kuvata hoitojen, ja erityisesti verenkiertoon vaikuttavien (vasoaktiivisten) lääkkeiden, toteutumista suhteessa ASV:n eri taudinkuviin ja erityisesti sydänperäisen shokkiin. Lisäksi tavoitteena on kuvata kaksi aiemmin huonosti tunnettua taudinkuvaa: 1) sepelvaltimotautikohtauksen aiheuttama ASV, ja 2) sydänperäinen sokki, jota komplisoi akuutti munuaisvaurio, joka on yleinen kriittisesti sairailla.

Väitöskirjassa käytetään kahta itsenäistä etenevää monikeskustutkimusta: 1) kansallista FINN-AKVA-tutkimusta, joka keräsi 620 sairaalahoitoon joutunutta ASV-potilasta; ja 2) eurooppalaista CardShock-tutkimusta, joka pitää sisällään 219 eri taudinsyistä johtuvaa sydänperäistä shokkia potevaa potilasta.

Furosemidi oli useimmin käytetty hoito riippumatta taudinkuvasta, ja sitä käytettiin usein myös sydänperäisen sokin varhaisvaiheessa. Muiden ASV:n hoitojen käyttö vaihteli taudinkuvan mukaan. Systolinen verenpaine oli yksi tärkeimmistä hoidon toteutumista ennustavista tekijöistä. Nitraattien käyttö vaikutti alimitoitetulta eurooppalaisiin hoitosuosituksiin nähden erityisesti korkean verenpaineen aiheuttamassa ASV:ssa.

Sepelvaltimotautikohtauksen aiheuttama ASV ilmeni vakavammalla taudinkuvalla. Suositusten mukaisia ASV-hoitoja ja kajoavia sepelvaltimotoimenpiteitä tehtiin myös useammin, mutta siitä huolimatta sepelvaltimoiden varjoainekuvausten (35%) ja verenkierron palauttamiseen tähtäävien toimenpiteiden (pallolaajennus 16% ja ohitusleikkaus 10%) määrä oli matala. Sepelvaltimotautikohtauksen aiheuttamaan ASV:aan liittyi selvästi lisääntynyt 30 päivän kuolleisuus (13% vs 8%).

Vasopressorien ja inotrooppien käyttö oli melko yleistä myös muilla kuin sokkipotilailla ja etenkin akuutissa keuhkopöhössä sekä sepelvaltimotautikohtauksen aiheuttamassa ASV:ssa. Sydänperäisessä sokissa yleisin vasopressori oli noradrenaliini kun taas dobutamiini oli yleisin inotrooppi. Adrenaliiniin käyttöön liittyi ylenpalttinen sydänvaurio ja 90 päivän ylikuolleisuus. Sen sijaan yhdistelmiin noradrenaliini-dobutamiini ja noradrenaliini-levosimendaani liittyi myönteisempi ennuste.

Sydänperäisessa sokissa kehittyi usein akuutti munuaisvaurio 48 tunnin sisällä shokin alusta, mutta ilmaantuvuus vaihteli akuutin munuaisvaurion määritelmien välillä. Virtsantuloon perustuva määritelmä vaikutti melko löyhältä eikä se ollut yhteydessä lisääntyneeseen 90 päivän kuolleisuuteen

toisin kuin kreatiniini- ja kystatiini C-määritelmät. Tiukempi virtsantulon raja-arvo, <0.3 ml/kg/h 6 tunnin ajan, oli tarkempi kuolleisuuden ennustamisessa. Akuutti munuaisvaurio oli yhteydessä matalaan verenpaineeseen ja sydämen minuuttitilavuuteen sekä laskimotungokseen viittaaviin löydöksiin.

Yhteenvetona voidaan todeta, että vasoaktiivisten lääkehoitojen toteutuminen on yhteydessä ASV:n kliiniseen luokitukseen, alkuvaiheen systoliseen verenpaineeseen ja sepelvaltimotautikohtaukseen ASV:n aiheuttajana. Nitraattien käyttö oli odotettua vähäisempää kun taas vasopressorien ja inotrooppien käyttö vaikutti liialliselta. Adrenaliinin käyttöön liittyi huomattava sydänvaurio ja ylikuolleisuus. Samanaikainen sepelvaltimotautikohtaus ASV:ssa vaikutti lisäävän lyhyen aikavälin kuolleisuutta, kun taas akuutti munuaisvaurio liittyi huonoon ennusteeseen sydänperäisessä sokissa.

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Tuukka Tarvasmäki

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Tarvasmäki T, Harjola V-P, Tolonen J, Siirilä-Waris K, Nieminen MS and Lassus J; FINN-AKVA Study Group. Management of acute heart failure and the effect of systolic blood pressure on the use of intravenous therapies. Eur Heart J Acute Cardiovasc Care. 2013;2(3):219-25.

II Tarvasmäki T, Harjola VP, Nieminen MS, Siirilä-Waris K, Tolonen J, Tolppanen H, Lassus J; FINN-AKVA Study Group. Acute Heart Failure With and Without Concomitant Acute Coronary Syndromes: Patient Characteristics, Management, and Survival. J Card Fail. 2014;20(10):723-30.

III Tarvasmäki T, Lassus J, Varpula M, Sionis A, Sund R, Køber L, Spinar J, Parissis J, Banaszewski M, Silva Cardoso J, Carubelli V, Di Somma S, Mebazaa A, Harjola VP; CardShock study investigators. Current real-life use of vasopressors and inotropes in cardiogenic shock – adrenaline use is associated with excess organ injury and mortality. Crit Care. 2016;4;20(1):208.

IV Tarvasmäki T, Haapio M, Mebazaa A; Sionis A, Silva-Cardoso J, Tolppanen T, Lindholm MG, Pulkki K; Parissis J, Harjola V-P, Lassus J; CardShock study investigators. Acute kidney injury in cardiogenic shock – definitions, incidence, hemodynamic alterations, and mortality. Eur J Heart Fail. 2017. DOI: 10.1002/ejhf.958. E-pub ahead of print.

ABBREVIATIONS

95% CI = 95% confidence interval
ACEi = angiotensin-converting-enzyme inhibitor
ACS = acute coronary syndrome
ACS-AHF = acute heart failure with concomitant acute coronary syndrome
ADHF = acute decompensated heart failure
AHF = acute heart failure
AKI = acute kidney injury
AKI_{crea} = acute kidney injury by creatinine definition
AKI_{CysC} = acute kidney injury by cystatin C definition
AKI_{UO} = acute kidney injury by urine output definition
AMI = acute myocardial infarction
AMI-CS = cardiogenic shock complicating acute myocardial infarction
awCHF = acute worsening of chronic heart failure
ARB = angiotensin receptor blocker
AUC = area under the curve
CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CI = cardiac index
CO = cardiac output
CVP = central venous pressure
CysC = cystatin C
CS = cardiogenic shock
EF = ejection fraction
eGFR = estimated glomerular filtration rate
ESC = European Society of Cardiology
FINN-AKVA = Finnish Acute Heart Failure Study
GFR = glomerular filtration rate
HF = heart failure
HR = hazard ratio
IQR = interquartile range
IABP = intra-aortic balloon pump
ICU = intensive care unit
KDIGO = Kidney Disease: Improving Global Outcomes
LV = left ventricular
LVEF = left ventricular ejection fraction
MAP = mean arterial pressure
MI = myocardial infarction
nACS-AHF = acute heart failure without concomitant acute coronary syndrome
NIV = non-invasive positive pressure ventilation
NT-proBNP = N-terminal pro-B-type natriuretic peptide

OR = odds ratio
PE = pulmonary edema
RAAS = renin-angiotensin-aldosterone system
RV= right ventricular
SBP = systolic blood pressure
SD = standard deviation
STEMI = ST-elevation myocardial infarction
TnT = troponin T
WRF = worsening renal function

1 INTRODUCTION

Acute heart failure (AHF) is a frequent cause for hospitalization and consumes a significant proportion of health care expenditures in Western countries.[1,2] Although chronic heart failure has been extensively studied and modern treatment has improved patient outcomes, AHF — despite its clinical importance — has received less attention and is persistently associated with poor short- and long-term prognosis.[3-6]

Management of AHF is difficult, due to a mixture of heterogeneous clinical manifestations. In order to better understand and assess the spectrum of AHF, the disease can be classified on the basis of clinical presentation. In terms of outcome, cardiogenic shock (CS) carries the poorest prognosis, whereas nearly all patients with hypertensive AHF are discharged alive from hospital.[6,7] This also reflects the importance of systolic blood pressure (SBP) as a prognostic factor for outcome, as it has been inversely associated with mortality risk.[4,8,9]

Several conditions may precipitate AHF, including acute coronary syndrome (ACS), atrial fibrillation, valvular disease, infection, and also lack of compliance with medication or with lifestyle advice. Generally, ACS is a major cause of AHF in up to one-third or even a higher proportion of AHF patients.[7,10-13] However, ACS patients often have either been excluded from AHF trials or not considered as their own entity, and data comparing characteristics, management, and outcome between AHF patients with (ACS-AHF) and without ACS (nACS-AHF) is scarce. Filling this gap in knowledge could help us understand differences between these two entities and possibly improve patient outcomes.

The most devastating form of both AHF and ACS is CS, which is associated with extremely poor prognosis. Fortunately, the incidence of CS is low, occurring in around 4% or less of AHF patients.[4,6,7,14-16] Although CS incidence has declined, and increased utilization of early revascularization has improved outcomes in CS caused by acute myocardial infarction (AMI-CS), short-term mortality is still high, up to 40-50%.[17-22] However, although CS has numerous other possible causes, regrettably, most data on CS rely on studies and registries including only AMI-CS patients.

The heart and the kidneys in heart failure (HF) are tightly interconnected, and worsening renal function (WRF) plays an important role in deterioration of prognosis. Likewise, in hospitalized patients acute kidney injury (AKI) is a common problem especially frequent among the critically ill, in whom it is the most common cause of organ failure, with a prevalence exceeding two-thirds of patients.[23-27] The current definition of AKI include criteria for increased creatinine level and reduced urine output (UO). Despite the abundant literature on AKI, UO criteria have often been omitted or modified.

In particular, study of the clinical importance and utility of contemporary definitions of AKI in CS is meagre.

Difficulty in determining optimal AHF management is related to its wide spectrum of clinical presentations, but also regrettably to the paucity of robust data showing any beneficial effect from available pharmacotherapies, reflected by the fact that the pharmacotherapies and other treatment options have remained generally unchanged for decades. Nevertheless, diuretics and vasodilators have remained the standard medications in most forms of AHF for the same lengthy period. They should be preferred over the inotropic and vasopressor agents, which are recommended for correction of hypotension and for promoting cardiac output (CO) to ensure adequate perfusion for organs and tissues; inotropes and vasopressors should be avoided in AHF without hypoperfusion and shock.[28] Adherence to guideline-recommended therapies has improved outcome in chronic HF,[29,30] and analogously, in AHF, either under- or over-treatment may lead to adverse outcomes.

To improve adherence to guideline recommendations and avoid harm by under- or overuse of treatment modalities, and thus possibly improve patient outcome, we need better understanding of the current status of AHF management in clinical practice taking into account differing clinical profiles. In particular, the clinical profile of ACS-AHF needs detailed description, and the clinical importance of AKI, as the main acute organ failure in the critically ill, must be examined in CS.

The aim of this thesis is to study these questions by use of material from two prospective studies: the FINN-AKVA study comprising an AHF population from Finland, and the European multicenter CardShock study.

2 REVIEW OF THE LITERATURE

2.1 ACUTE HEART FAILURE

2.1.1 DEFINITION

Heart failure is a clinical syndrome featuring as typical symptoms and signs: shortness of breath during exercise or at rest, fatigue, swelling of the lower extremities, pulmonary congestion, and elevated jugular venous pressure.[28] Objective evidence is essential of a cardiac cause for these symptoms: structural or functional abnormality of the heart resulting in inadequate CO or elevated intracardiac pressures, or both. Usually, this is a result of myocardial dysfunction, which may be either systolic or diastolic, or both. The current ESC guidelines divide HF into three categories by left ventricular ejection fraction (LVEF): normal LVEF (≥50%) is HF with preserved ejection fraction, reduced LVEF (<40%) is HF with reduced ejection fraction, and LVEF between these two (40-49%) is HF with a mid-range ejection fraction.[28] In addition to impaired myocardial function, HF can result from abnormalities of the valves, pericardium, endocardium, heart rate and rhythm, and conduction. HF is never a sole diagnosis, and because the underlying abnormality determines appropriate therapy, the precise pathology should always be sought.[28]

The term "acute HF" can mean either a temporal association (new-onset HF) or refer to disease severity (medical emergency resulting in hospitalization). To include both aspects, AHF is defined here either as 1) emergence of new-onset, or *de novo*, AHF *or* 2) acute decompensation, or acute worsening, of chronic HF (awCHF), each resulting in hospitalization. The acuteness may, however, vary, because the time-range for symptom deterioration may be from minutes to hours—for instance, in AHF caused by acute myocardial infarction (AMI) or arrhythmia—and even to weeks (for example non-adherence to therapy).[31]

2.1.2 EPIDEMIOLOGY

Large-scale registries have provided insight into AHF epidemiology: the largest registries such as ADHERE and OPTIMIZE-HF are from the United States and the EHFS-I, EHFS-II, and ESC-HF Pilot registries have collected data from Europe.[7,14,32-35] In addition, several national and international studies such as the Italian IN-HF Outcome study and the international ALARM-HF have provided a considerable input of knowledge.[4,11,36]

In developed countries, HF prevalence is around 1-2% of the adult population, rising to ≥ 10% among those ≥ 70 years of age.[28] AHF represents

1% to 2% of all hospitalizations.[1] On average, AHF patients are over 70, and half are women. About one-third, and in some studies up to half the patients hospitalized have *de novo* AHF, with at least half thus having an HF history.[16,37]. Typically, the most common cardiovascular comorbidities include hypertension, coronary artery disease (CAD), and atrial fibrillation, with diabetes mellitus, chronic obstructive pulmonary disease, and renal insufficiency the most frequent among non-cardiovascular comorbidities.[16,37]

2.1.3 PATHOGENESIS AND ETIOLOGY

Acute heart failure constitutes a heterogeneous clinical syndrome with a complex and highly variable pathophysiology.[37] Several differing mechanisms along with factors triggering decompensation are involved.[38,39] The main cause is heart dysfunction resulting in reduced CO, increased filling pressures, and augmented afterload. Background phenomena for abnormalities in the myocardium include a) neurohormonal activation, which includes the activation of the following pathways and systems: the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, arginine vasopressin, endothelin, adrenomedullin, and the system of natriuretic peptides; b) inflammatory reactions, and c) oxidative stress. These mechanisms are primarily adaptive but become maladaptive and detrimental when sustained. They are related, for example, to cardiomyocyte hypertrophy and apoptosis, depressed myocardial contractility, fibrosis, and remodeling.[39] Neurohormonal activation leads to vasoconstriction, sodium and water retention, redistribution, and increased diastolic filling pressures. Elevated left ventricular (LV) filling pressures may result in change in LV geometry (remodeling), which often exacerbates functional mitral insufficiency, further reducing CO.[37]

Myocardial injury may occur due to an ischemic event, e.g. ACS, hemodynamic abnormalities, or neurohormonal activation. Additionally, oxygen supply-demand mismatch may result as a consequence of increasing LV diastolic pressure and LV wall stress, further activation of neurohormones, or inotropic stimulation;[40] patients with CAD and hibernating myocardium or ischemic myocardium, or both, are especially prone to injury precipitated by these conditions.[38]

Regardless of the cause, high LV diastolic pressure results in pulmonary venous congestion, and further interstitial and alveolar edema. High right atrial pressure resulting in systemic (venous) congestion and peripheral edema is usually caused by high left-sided pressures,[38] but may also be caused by primary right ventricular (RV) failure.

In addition to myocardial dysfunction, AHF is characterized by systemic endothelial dysfunction related to nitric-oxide-dependent regulation of vascular tone.[37] This dysfunction may result from imbalance in the neurohormonal, oxidative, or inflammatory environment in the circulation and in endothelial cells,[39] and it may lead to reduced coronary flow and

myocardial ischemia. In addition, arterial stiffness and impaired arterial distensibility worsen cardiac loading conditions and aggravate myocardial damage.[37,39]

Peripheral vasoconstriction redistributes blood centrally, thus increasing central venous pressure (CVP), pulmonary venous congestion, and edema. Peripheral arterial vasoconstriction elevates afterload, LV filling pressures, and postcapillary pulmonary venous pressures. Increase in afterload worsens myocardial wall stress, myocardial ischemia, and cardiac arrhythmias. LV diastolic dysfunction worsens the effects of vascular abnormalities.[37] Endothelial dysfunction may cause a secondary increase in sympathetic drive and catecholamine release.[39]

Renal impairment plays an important role in AHF pathophysiology by modulating loading conditions of the heart because of renal control over intravascular volume; such impairment is responsible for neurohormonal output.[37] Structural kidney dysfunction may result from diabetes mellitus, hypertension and arteriosclerosis, all of which are frequent in HF patients. Worsening renal function (WRF) often occurs during AHF and may result from neurohormonal abnormalities, endothelial dysfunction, or hemodynamic alterations. Reduced CO and venous congestion result in reduced glomerular filtration rate (GFR).[37,41] Renal impairment, in turn, leads to disturbances in the sodium and water homeostasis, and to activation of neurohumoral pathways; AHF itself causes activation of the sympathetic nervous system, and RAAS, as well.[42,43] These mechanisms promote fluid retention, increased vascular resistance and further congestion. In addition, unwanted drug effects may aggravate WRF; high-dose loop diuretics can, for instance, activate neurohormonal pathways, causing sodium and water retention and increased vasoconstriction, further reducing renal blood flow.[37]

The main precipitating factors include ACS (presenting as MI, or unstable angina), acute arrhythmia, valvular regurgitation (endocarditis, rupture of chordae tendinae, worsening of existing aortic, mitral, or tricuspid regurgitation) or stenosis (severe aortic stenosis), infection (pneumonia, sepsis), and medical or dietary noncompliance. Other factors include uncontrolled hypertension, myocarditis, acute pulmonary embolism, cardiac tamponade, anemia, worsening renal function and drugs such as nonsteroidal anti-inflammatory agents.[16,28] For patients with normal myocardium and myocardial function a substantial disturbance in cardiac performance (acute myocarditis, ACS) is required to lead to AHF whereas in patients with abnormal myocardial function (chronic HF, structural heart disease), smaller disruptions (uncontrolled hypertension, atrial fibrillation, infection) may precipitate AHF episode.[37]

2.1.4 CLASSIFICATIONS

AHF presents as a combination of a wide spectrum of conditions, in which each classification has its strengths and limitations. Classifications are also useful in guiding AHF management. One classification similar to that of the ESC guidelines,[44] based on to the condition's clinical presentation:

- Cardiogenic shock: evidence of tissue hypoperfusion (e.g. oliguria, confusion, lactatemia, cold periphery) and low blood pressure (SBP <90 mmHg or need of vasopressors to sustain perfusion) induced by HF after correction of preload.
- Pulmonary edema (PE; verified by chest xray) accompanied by severe respiratory distress, with crackles over the lung and orthopnoea, with O2 saturation usually 90% on room air
- Acute decompensated heart failure: signs and symptoms of AHF that are mild and do not fulfill criteria for cardiogenic shock, PE or hypertensive crisis
- Hypertensive AHF: Signs and symptoms of heart failure accompanied by high blood pressure and relatively preserved left ventricular function with a chest radiograph compatible with PE
- Right HF: AHF predominantly due to RV failure with signs and symptoms of decreased CO, increased jugular venous pressure with distension of the jugular vein, increased liver size, and severe edema

This classification may be supplemented with AHF with concomitant ACS (ACS-AHF) as in the ESC 2008 HF guidelines,[45] but this category often presents with one of the above manifestations. High-output failure has also been used,[44] but this condition is not a result of cardiac function abnormality, and it is characterized by extreme hemodynamic requirement and high CO.

Although not included in the current ESC guidelines, the clinical classification, with or without ACS-AHF, is still actively used in the contemporary literature.[6] The current guidelines include, however, the same information as in the clinical classification for clinical profiling in treatment guidance; for details, see section 2.4. The main clinical classifications are summarized in Figure 1.

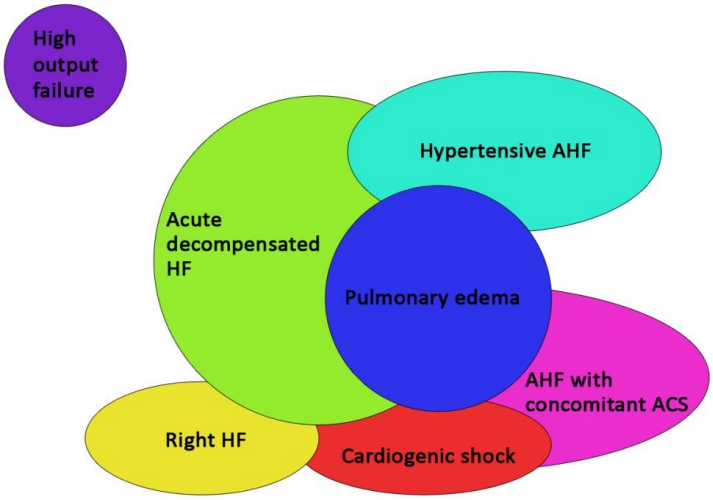

Figure 1 Clinical classification of AHF. Modified with permission from Springer.[46]

Hemodynamic profiling,[28] modified from the Forrester classification dating from the 70s,[47] allows assessment of clinical signs/symptoms of congestion ("wet" vs "dry") and peripheral hypoperfusion ("cold" vs "warm").[28,48] The combination of these options produces four groups: warm-dry, warm-wet, cold-dry, and cold-wet.

AHF may also be classified according to blood pressure at presentation. SBP overlaps with other classifications: for example, SBP is lowest in CS and in hypoperfusion (i.e. in those that are "cold" in hemodynamic profiling) and highest in hypertensive AHF.

2.1.5 PROGNOSIS AND PREDICTORS OF MORTALITY

Overall, patients with AHF have a poor prognosis. Although their in-hospital mortality (4-7%) is similar or higher than that of AMI patients,[4,16,49] their long-term mortality is much worse, and around 60% are dead in five years.[50-53] In addition to high mortality, rehospitalization rates are high.[1,2]

Numerous factors are identifiable in AHF as predictors of mortality, and several risk scores exist. Risk scores include old age, high heart rate, low SBP, impaired renal function (elevated creatinine or cystatin C (CysC)), and low sodium level among other factors predicting poorer outcome.[54-58] Low SBP at presentation, contrary to what is observed in a "normal" population, deserves special emphasis as a significant predictor of poor short- and long-term outcome.[3,4,6,9,36,53,59] Classification of AHF by SBP at presentation is thus also predictive of mortality. Analogously, mortality differs among the clinical presentations: patients with CS have very high short-term mortality, with an in-hospital and 30-day mortality of up to 40-50%.[17-22] Lower in-hospital mortality, in decreasing order, includes PE (6-9%), right HF (6-9%), ADHF

(4-5%), and hypertensive AHF with the lowest mortality (1-3%).[4,6,7] In addition, hemodynamic profiling involving congestion and perfusion status provides information on outcome; [6,48,60] a connection with SBP also exists, because "cold" or hypoperfused patients experience the lowest blood pressure.

Patients with awCHF have significantly worse long-term prognosis than do those with *de novo* AHF.[52,61]

2.2 ACUTE HEART FAILURE WITH CONCOMITANT ACUTE CORONARY SYNDROME

Acute coronary syndrome refers to a spectrum of clinical presentations ranging from unstable angina pectoris (UAP) to non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) caused by myocardial ischemia. The main etiology is CAD, with most cases of ACS resulting from atherosclerotic plaque disruption leading to decreased blood flow followed by myocardial ischemia and, in myocardial infarction (MI), subsequent myocardial necrosis (type I MI). The main symptom is chest pain with or without additional symptoms such as sweating, nausea, dyspnea, and abdominal pain. Chest pain may also be absent, and especially the elderly and patients with diabetes may show atypical symptoms such as epigastric pain or isolated dyspnea. In addition to assessment of symptoms and clinical findings, which may be somewhat unremarkable, the diagnosis of ACS includes an electrocardiogram (ECG), the first-line diagnostic tool.[62] Biomarkers, preferably high-sensitivity cardiac troponin, complement the diagnosis, risk assessment, and treatment.[62,63]

Coronary artery disease is an underlying disease in half to two-thirds of AHF, [7,10,11,13,53] although this may be an underestimation; most studies lack systematic coronary anatomy assessment.[64] Likewise, ACS is an important precipitating factor for AHF, and an incidence of one-third or even a larger proportion of patients. [6,7,10,11,13,53]

Patients admitted to the hospital with ACS may already present with concomitant AHF on admission or develop it in the hospital; thus, myocardial injury (type I MI) is the principal cause for AHF, but myocardial injury may result from worsening HF, at which time a mismatch occurs in oxygen delivery and demand (type II MI). Underlying mechanisms may include subendocardial ischemia resulting from high ventricular diastolic pressure and wall stress, activation of neurohormones resulting in increase in cardiac contractility and oxygen consumption, and reduction in coronary perfusion through endothelial dysfunction.[40]

Additionally, myocardial hibernation and stunning are frequent among patients with HF and CAD.[65] Impairment and exhaustion in the autoregulation between coronary artery perfusion and coronary vasoactive tone is also a possibility.[66] Not only hypotension, anemia, and impaired

hemodynamics, but also use of inotropic medications may further aggravate the supply-demand mismatch[40], and, in hibernating myocardium, disrupt adaptive mechanisms[67,68] or even precipitate MI.[69] The resulting myocardial injury is detectable as cardiac troponin elevation. Such troponin elevations in AHF may, however, result from non-ischemic events, which include proteolysis of myocardial contractile proteins, myocardial apoptosis and autophagy, both due to wall stress, and direct toxicity of neurohormones.[40]

A considerable amount of data shows that complicating HF in the setting of ACS carries a substantial increase in mortality risk.[64] In comparison, studies in the setting of AHF have reported conflicting results as to the effect of ACS on survival.[3,4,9,10,70,71] Despite being a significant precipitating factor of AHF and possibly a predictor of poor prognosis, ACS has either been excluded from AHF trials or has been considered as not in itself a distinct clinical entity. Thus, few studies have specifically compared ACS-AHF and nACS-AHF patients.[12,71]

2.3 CARDIOGENIC SHOCK

2.3.1 DEFINITION

Cardiogenic shock is often defined as a state of tissue and end-organ hypoperfusion due to cardiac dysfunction (impaired function of myocardium, valves, conduction system, pericardium) and reduced output in the presence of adequate intravascular volume.[72-74] The spectrum of presentation ranges from mild hypoperfusion to profound and refractory shock. Common clinical criteria include hypotension, often defined as SBP <90 mmHg for 30 min (despite adequate fluid challenge or in the absence of hypovolemia) *or* need for vasopressor therapy to maintain SBP >90 mmHg, *and* end-organ hypoperfusion, defined as cold extremities, oliguria, altered mental status, and lactatemia.[19,20,75,76] For the CS diagnosis, studies have included and experts recommended signs of pulmonary congestion and hemodynamic criteria such as reduced cardiac index (CI) (<2.2 l/min/m^2), and pulmonary capillary wedge pressure > 15 mmHg[75,76] or right ventricular end-diastolic pressure >10-15 mmHg.[77] However, recent expert recommendations have relied on clinical criteria without invasive hemodynamic measurements;[78,79] this was the approach of the largest randomized controlled in CS to date, the IABP-SHOCK II trial.[19]

2.3.2 EPIDEMIOLOGY, ETIOLOGY, AND PROGNOSIS

ACS, of which the majority is STEMI, is the most common cause of CS, accounting for 80% of cases.[80] Conversely, around 5-8% of AMI cases are complicated by CS.[17,18,81] With regard to AHF, patients in CS account for only a minority of patients (typically around 3-5%).[4,6,7,14,15] Most cases are attributable to predominant LV failure, and only a minority (5%) present with isolated RV shock.[82] Mechanical complications such as ventricular free wall or septal rupture, and acute severe mitral valve regurgitation are also a frequent cause of CS.[80]

The rate of CS remained stable at 8-9% of STEMI patients between 1995 and 2004 in the NRMI database analysis from the USA,[17] while the Swiss AMIS Plus Registry reported that between 1997 and 2006 the decrease in CS complicating ACS was 12.9% to 5.5%.[18] A report from Sweden covering 1995 and 2002 showed a greater decline in the incidence of CS among patients with non-STEMI than among those with STEMI.[83] A recent Italian study on CS complicating ACS showed an increase in CS at admission from 1.9% to 2.7% and a decrease in number of patients developing shock during hospitalization from 4.8% to 2.1% between 2001 and 2014,[20] whereas two studies from the USA have reported their incidence of pre-hospital shock to have remained stable but of in-hospital CS to have decreased.[21,84] Shock is not present in the majority of patients on admission and occurs mostly during the first 24 hours.[17,18,20,21,85]. Typical reported predictors of CS-AMI are older age, signs of HF at admission, anterior location of infarction, and a history of HF, MI, CABG, or diabetes mellitus.[83,86,87]

Since the majority of CS results from ACS, most CS studies are based on registry data concerning patients with ACS or MI. Although a significant proportion of patients do have other etiologies, contemporary data on CS including patients with various etiologies have been scarce. The reason may be that the landmark SHOCK trial dates back to the 1990's,[80] and the more recent IABP-SHOCK II trial included only patients with MI.[19] In fact, numerous other causes exist: worsening of chronic HF, such as dilated cardiomyopathy, myocarditis (viral, giant cell, eosinophilic), Takotsubo cardiomyopathy, arrhythmias including CS following cardiac arrest, procedural complications (surgical, cardiac catheterization complications, postcardiotomy CS) and iatrogenic CS resulting from such factors as excessive β or Ca^{2+} channel blockade. In addition, massive pulmonary embolism may result in isolated RV shock.[72,73]

Although advances in treatment mainly by early revascularization have had a positive impact on patient survival, short-term and overall mortality is still uacceptably high, around 40-50%.[17-20,22,81] Typical factors associated with higher mortality are older age, history of coronary artery bypass graft surgery (CABG), altered mental status, lower systolic blood pressure, lower left ventricular ejection fraction (LVEF), poor renal function, and higher blood lactate.[88,89] Impaired microcirculation is also a significant predictor of poor outcome.[90]

2.3.3 PATHOPHYSIOLOGY

Regardless of the CS etiology, inadequate CO leads to end-organ hypoperfusion. Usually the cause is a large MI, but other sources of myocardial injury also cause systolic dysfunction resulting in decreased stroke volume and CO, increased ventricular diastolic pressure and wall stress, all of which further reduce coronary perfusion pressure and aggravate ischemia. In addition, exacerbation of diastolic dysfunction elevates LV diastolic and left atrial pressure, leading to pulmonary congestion, hypoxia, and worsening ischemia.[72,73]

Furthermore, sympathetic tone increase due to compensatory neurohormonal responses results in increased heart rate and contractility, and in stimulation of the RAAS, which leads to fluid retention, increased preload, and vasoconstriction.[73] Large infarction and prolonged hypoperfusion often leads to an increase in systemic inflammatory response, resulting in the release and activation of inducible nitric oxide synthase; this further stimulates pathological vasodilatation and worsens hypotension and hypoperfusion.[91-93] An extensive inflammatory response is associated with poor prognosis regardless of concomitant infection or preceding cardiopulmonary resuscitation.[94] The downward spiral leads to end-organ dysfunction, such as AKI, and eventually to death (Figure 2).

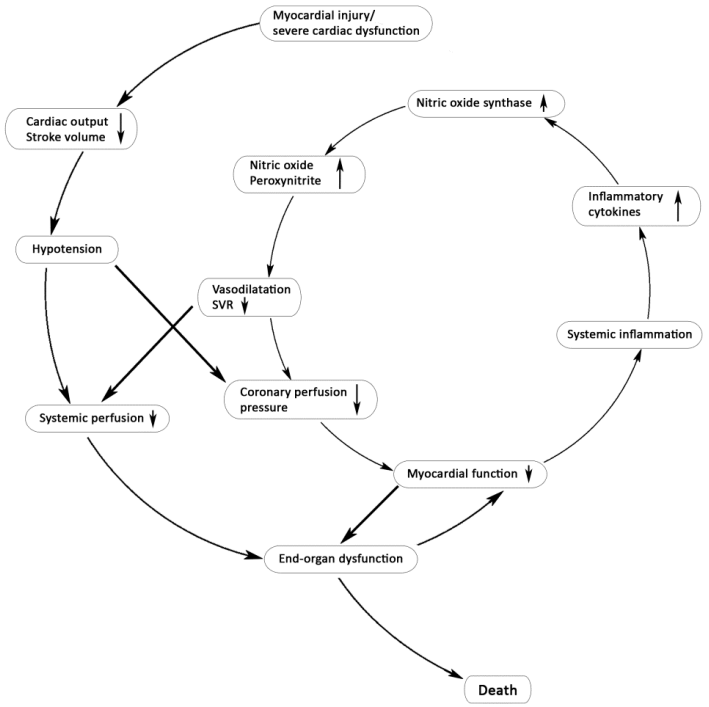

Figure 2 The downward spiral of cardiogenic shock. SVR = systemic vascular resistance. Adapted by permission of Macmillan Publishers Ltd.[73]

2.3.4 DIAGNOSIS

Diagnosis of CS is based on the clinical criteria already mentioned. While invasive hemodynamic assessment by pulmonary artery catheter may be useful in confirming and characterizing the shock, its routine use is not recommended for the diagnosis; it is useful in monitoring of hemodynamics or is reserved for patients in refractory shock.[28,63,74,78] Echocardiography is essential for evaluation of myocardial function and mechanical complications,[28,74] and may prove useful in hemodynamic evaluation.[74,78]

2.4 MANAGEMENT OF ACUTE HEART FAILURE

2.4.1 DIAGNOSIS AND INITIAL EVALUATION

Diagnosis of AHF is based on thorough assessment of medical history and on signs and symptoms of congestion or hypoperfusion, or both, by physical examination. Fluid overload is typical, manifesting as pulmonary or peripheral edema, or both, but signs of peripheral hypoperfusion from reduced CO are less frequent. As the signs and symptoms of AHF are neither specific nor sensitive, the diagnostic workup requires additional investigation. Chest X-ray can be of value as it may reveal cardiomegaly or pulmonary congestion and edema, as well as pleural effusion. It is useful in diagnosing alternative symptom causes, such as pneumonia.[28] ECG is a routine study, and in patients with AHF it is seldom normal.[37] Echocardiography is essential in initial AHF evaluation with hemodynamic instability or CS; it is useful in all cardiac patients and should be considered in *de novo* AHF and in those with unknown cardiac function, preferably within the first 48 hours. Thoracic (lung) ultrasound is useful for assessment of interstitial edema and pleural effusion.[28]

The current mainstay of laboratory testing in diagnosing or ruling out AHF involves natriuretic peptides. Guidelines recommend their measurement in all patients with acute dyspnea and suspected AHF.[28] They have a high sensitivity but unfortunately are not specific. Additional laboratory assessments include cardiac troponins, which may be used not only for diagnosis but for prognosis evaluation as well. Routine tests also include also creatinine, electrolytes, glucose, and blood count, with arterial blood gas useful in selected patients. Troponin measurements are helpful in detection and diagnosis of ACS, although elevated levels are often observable in AHF overall.[40] Several other laboratory tests may be considered as well, especially for prognosis evaluation.[28]

Identification of the AHF-precipitating factor is an important step for initiating specific treatment to avoid further deterioration. One means to assess the most important precipitating factors is by the CHAMP mnemonic:

acute Coronary syndrome, Hypertensive emergency, Arrhythmias, acute Mechanical cause, and Pulmonary embolism. In addition, infection (sepsis, pneumonia, urinary tract infection), exacerbations of pulmonary diseases such as COPD or asthma, and anemia, among others, require attention and treatment.[28]

The initial AHF management includes intravenous pharmacological therapies such as diuretics, vasodilators, opioids, inotropes, and vasopressors, and ventilatory support with oxygen, non-invasive ventilation, or invasive mechanical ventilation.

2.4.2 PHARMACOLOGICAL THERAPY

2.4.2.1 Diuretics

Diuretics, a cornerstone of AHF therapy, in guidelines are the first-line therapy in patients with signs or symptoms of congestion or fluid overload,[28,95,96] and they are the choice for up to nine of ten AHF patients.[4,7,11,14,15,36,97,98] Standard are loop diuretics such as furosemide, bumetanide or torasemide. They inhibit the $Na^+/2Cl^-/K^+$ cotransporter in the thick ascending loop of Henle, resulting in decreased urine sodium and chloride reabsorption with natriuresis and diuresis. In addition, loop diuretics also induce the synthesis of prostaglandins, resulting in renal and pulmonary vascular smooth muscle relaxation and venodilatation.[99] Intravenous (IV) administration results in venodilatation after 15 minutes, thus reducing the preload of both ventricles, and in a diuretic effect peaking at 30 minutes.[100] Eventually, left ventricular filling pressures decrease and symptoms are relieved.

On the other hand, loop diuretics activate the RAAS and the sympathetic nervous system, each plays a pivotal role in HF progression and in development of diuretic resistance. Activation of these systems and the related changes in renal blood flow and glomerular filtration pressure result in a GFR decrease. In addition, the homeostatic response to diuretic therapy counterbalances the diuretic effect by increasing sodium retention and thus preventing volume depletion. Moreover, persistent delivery of sodium or diuretics to the distal tubule leads to hypertrophy of the distal tubular cells, resulting in enhanced sodium retention. Delivery of diuretics to the site of action may be impaired by several mechanisms (impaired absorption from the gut, impaired secretion into the tubular lumen, increased reabsorption in the kidney, reduced drug availability in the tubular lumen). What is more, loop diuretics activate tubuloglomerular feedback, resulting in a decrease in GFR.[42] Left ventricular filling pressure and systemic vascular resistance may be increased and stroke volume decreased up to 1-2 hours after their administration.[101] Loop diuretics may lead to electrolyte imbalances such as hypokalemia, hyponatremia and hypomagnesemia. Furthermore, although

diuretics play a central role in relieving symptoms and congestion, no evidence on an effect on mortality has yet emerged.[102]

Given that rapid start of action is vital and that the rate of absorption of loop diuretics from a congested bowel is significantly decreased, loop diuretics are usually given intravenously. Data on optimal dosing, timing, and method of delivery are scarce. In the DOSE trial,[103] larger doses resulted in more marked improvement in dyspnea, and in greater loss of weight and fluid, at the cost of transient worsening of renal function. No differences in efficacy or safety appeared between bolus dosing and infusion. Thiazide diuretics, thiazide-like diuretics, and mineralocorticoid receptor antagonists may be combined with loop diuretics to cause increased diuresis or to overcome diuretic resistance; alternative approaches involve acetazolamide or hypertonic saline.[42]

2.4.2.2 Nitrates and other conventional vasodilators

Vasodilators, especially nitrates, comprise the second most frequently used medication for symptomatic relief,[4,7,11,15,36,97,98] and they have been administered to a majority of PE patients.[7,9,15] However, nitrate use shows geographical variation; they are less frequent in North America than other regions. In current ESC, Heart Failure Society of America (HFSA), and American College of Cardiology/American Heart Association (ACC/AHA) guidelines, vasodilators are to be considered for symptomatic relief in non-hypotensive AHF.[28,95,96] They should be considered as first-line medication in hypertensive AHF,[28,95,96] and — according to the US guidelines — also in PE [95] and mitral insufficiency to improve symptoms and relieve congestion.[96]

As most AHF patients present with increased left and right ventricular pressure and high or normal blood pressure, the use of nitrates (isosorbide mononitrate, isosorbide dinitrate, nitroglycerin, sodium nitroprusside) with filling-pressure-reducing effects would seem feasible. They are nitric-oxide donors, and nitric oxide binds to soluble guanylate cyclase, producing cyclic guanosine monophosphate and vascular smooth muscle relaxation.[104] Their half-life is short, 2-4 min for nitroglycerin in IV administration.[105] At the low doses usual in AHF, this effect produces pulmonary and systemic venodilation, increased capacitance, and a marked reduction in systemic preload. Both right and left ventricular pressures are reduced.

Afterload reduction, necessary, for example, in hypertensive AHF requires higher doses (nitroglycerin ≥150-250 μg/kg/min), resulting in dilation of arteries, including the coronary vasculature.[106] This effect may be more pronounced when systemic vascular resistance is severely elevated.[107] Additional effects include a reduction in cardiac-wall stress, myocardial oxygen demand, and degree of mitral regurgitation, as well as increase in myocardial perfusion and CO.[108] The main adverse effect is hypotension. In addition, nitrate use may be limited by nitrate tolerance, with attenuation of hemodynamic effects. To overcome this attenuation, doses may already

require an active increase within the first 12 hours of continuous use,[109,110] or by intermittent dosing.[111] Nitroprusside, a potent arterial and venous vasodilator, reduces myocardial oxygen demand and improves stroke volume and CO,[112] and proves particularly useful for any acute reduction in afterload (hypertensive AHF, acute aortic or mitral regurgitation). It may, however, cause hypotension, and — especially in patients with renal insufficiency and failure — prolonged use of high doses may produce thiocyanate toxicity.[104]

A Cochrane review on vasodilator therapies in AHF that compared nitrates with alternative interventions found no evidence of any difference in symptom relief or in hemodynamic variables. However, that review identified only four randomized controlled trials, ones of low quality.[113]

Other vasodilators currently available include nesiritide, a recombinant form of brain natriuretic peptide that has neurohormonal and vasodilator properties. The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial in hospitalized AHF patients requiring IV therapy showed a greater reduction in filling pressure with nesiritide when compared with the effect with nitrates, and more improvement in early dyspnea than from a placebo.[114] The ASCEND-HF trial, however, found no clinically meaningful or statistically significant beneficial effects on outcome with nesiritide compared with placebo, but the rate of hypotension was increased.[115]

2.4.2.3 Novel vasodilators

Despite the lack of evidence for nitrates or nesiritide, vasodilators as a part of AHF management are a topic of active research. Evidence is increasing that organ dysfunction associated with AHF is often related to congestion in the pulmonary vasculature and to venous congestion, which can be countered with novel vasodilators that reduce pulmonary pressure and CVP, thus reducing organ backpressure and improving organ perfusion.[116] Such new novel agents include serelaxin, a recombinant human relaxin-2 vasoactive peptide that causes systemic and renal vasodilation.[117] Although a post-hoc analysis of RELAX-AHF showed that early administration of serelaxin was associated with reduction in early worsening of HF and in 180-day mortality,[118] the recent RELAX-AHF-2 trial failed to meet its primary endpoints (cardiovascular mortality at 180 days or worsening heart failure through day five) and secondary endpoints (all-cause mortality at 180 days, length of hospital stay, or the combined endpoint of cardiovascular death or rehospitalisations due to heart/renal failure through day 180).[119]

Ularitide is another novel vasodilator subject to large multicenter trials now completed.[120] This drug is a synthetic form of urodilatin, which is a natriuretic peptide secreted by the kidney and considered an intrarenal paracrine regulator of sodium- and water homeostasis. IV administration of ularitide leads to systemic and renal vasodilation, diuresis, and natriuresis, and to inhibition of the RAAS. Unfortunately, recently published results from

the phase III trial showed no beneficial effect with ularitide on patient outcome.[121]

Other vasodilators under investigation include the calcium-channel blocker clevidipine, potassium-channel activator nicorandil, and nitroxyl donors.[116]

2.4.2.4 Opioids

Opioids relieve anxiety, pain, and dyspnea, and have been frequently used in PE treatment.[7,122] Side-effects including nausea, hypotension, and bradycardia, may increase the need for invasive ventilation, due to the depressive effect on respiration. They should be used with caution and not routinely due to the possibly elevated mortality risk in AHF.[28,123,124]

2.4.3 OXYGEN THERAPY AND VENTILATORY SUPPORT

Ensuring an adequate oxygen supply for hypoxemic AHF patients is essential, but oxygen therapy should not the choice for non-hypoxemic patients and hyperoxia during treatment should be avoided.[125] Positive expiratory end pressure in invasive mechanical ventilation reduces left ventricular pre- and afterload, which has beneficial effects on hemodynamics by means of an increase in CO in an afterload-dependent left ventricle.[126] In a preload-dependent situation such as hypovolemia or RV failure, however, caution is necessary, because positive expiratory end pressure may result in a CO decrease. Positive expiratory end pressure is also applied via non-invasive positive pressure ventilation (NIV), which alleviates symptoms, reduces the work of breathing, and improves hemodynamics,[127] likely by mechanisms similar to those of invasive ventilation.[126] Furthermore, NIV seems to reduce the need for intubation and reduces mortality.[127] However, of every ten patients with PE, only one seems to receive NIV.[9]

2.4.4 INITIATION AND CONTINUATION OF EVIDENCE-BASED ORAL THERAPIES

Evidence-based oral therapies in (chronic) HF include β blockers, ACEis, angiotensin-receptor blockers (ARB), mineralocorticoid receptor antagonists and angiotensin-receptor neprilysin inhibitor (ARNI). Their mortality-reducing effects have been apparent in heart failure with reduced ejection fraction. In patients with awCHF, none of the medications should be discontinued on admission or during hospitalization unless hemodynamic instability or hypoperfusion persists.[28] In case of hyperkalemia or severe renal insufficiency, the dosage of ACEis, ARBs, mineralocorticoid receptor antagonists, and angiotensin-receptor neprilysin inhibitor may be reduced or the medication temporarily discontinued; however, β blockers can be safely

continued except in CS. Discontinuation of β blockers in AHF has been associated with increased mortality and re-hospitalization.[128]

Initiation of evidence-based oral therapies is recommended as soon as possible after hemodynamic stabilization. ACEis and β blockers are the first-line medications and can be started simultaneously, the initial low doses being gradually up-titrated to the maximum tolerable dose.[28]

2.4.5 TREATMENT OF ACUTE CORONARY SYNDROME IN AHF

Acute coronary syndrome, whether it is unstable angina pectoris, non-STEMI or STEMI, should be managed according to current guidelines. Treatment includes antiplatelet medication including acetylsalicylic acid and adenosine diphosphate-receptor blockers, and also include anticoagulants and high-dose statins. β blockers and ACEi/ARBs should be initiated after hemodynamic stabilization in all patients with systolic dysfunction or HF.[62]

When both ACS and AHF coexist, current guidelines recommend an immediate (<2 h after hospital admission) invasive strategy aiming for revascularization.[28,62,63] With regard to pharmacological AHF therapy, guidelines are, however, few and mixed. ESC guidelines include class I recommendations for nitrates when ACS/STEMI is complicated by AHF,[62,63] whereas HF guidelines do not specifically mention nitrates in AHF with concomitant ACS.[28]

Studies have suggested that ACS patients with complicating AHF are less likely to receive recommended therapies or even to undergo invasive strategy than are patients with solely ACS. [129-133] Although early angiography and revascularization are likely to lead to increased use of recommended and prognostically beneficial cardiac medications, and to improve patient outcomes also in AHF patients,[134] rates for invasive strategies in AHF studies have consistently been considered rather low overall.[4,7,135,136] However, comparative data on medical or invasive treatment between AHF patients with and without ACS have been scarce.[12,71]

2.5 MANAGEMENT OF CARDIOGENIC SHOCK

2.5.1 ASSESSMENT OF ETIOLOGY

All patients with CS should be evaluated for its etiology: ECG, chest xray, and echocardiography are essential.[74] All treatable etiologies should be managed promptly. AMI warrants early revascularization, whereas acute severe valvular causes and mechanical complications of MI need surgery.

2.5.2 ANGIOGRAPHY AND REVASCULARIZATION

In CS that is complicating ACS/AMI, immediate angiography and revascularization is the most important treatment strategy. In the SHOCK trial, patients with AMI-CS were randomly assigned to initial medical stabilization or early revascularization. Although the primary endpoint, 30-day mortality, did not statistically differ between the initial medical stabilization and early revascularization group (56 % vs 47%), a significant decrease in mortality occurred after six months (50% vs. 63%, p = 0.027), with the difference in the early revascularization group persisting at one and six years.[75,137] Current guidelines recommend early revascularization, either by percutaneous coronary intervention (PCI) or CABG depending on coronary anatomy, with a class I recommendation.[28,62,63,138] Revascularization should be performed as soon as possible but the time window for survival benefit may be up to 18 hours after shock onset.[139] If revascularization is unavailable and mechanical complications have been ruled out, fibrinolysis is an option in STEMI.[63]

2.5.3 MANAGEMENT OF HEMODYNAMIC INSTABILITY

In the critically ill and in all shock states, fluid resuscitation is a critical part of hemodynamic stabilization. As at least relative hypovolemia often exists in CS as well, prompt initial fluid therapy to correct hypovolemia, improve microvascular blood flow, and optimize right ventricular preload to elevate CO. [140,141] On the other hand, excess fluid resuscitation may lead to and worsen congestion (venous, pulmonary, peripheral), resulting in PE, AKI, RV dilation, worsening of CO, RV endocardial ischemia, and ischemic hepatitis among other detrimental consequences.[140] Unfortunately, no randomized controlled trials have investigated fluid therapy in CS, but trials involving other critical illnesses, such as septic shock, have suggested that liberal fluid therapy could be harmful, whereas a convervative approach is associated with increased ventilator-free days and decreased length of ICU stay.[140,142] In addition, one retrospective observational study reported recently that in CS, an accumulation of fluids and positive fluid balance is associated with increased mortality.[143]

If the initial fluid resuscitation fails to correct hemodynamics, vasoactive medication should be initiated to restore adequate perfusion pressure and CO. An initial target mean arterial pressure (MAP) of 65(-70) mmHg is considered adequate in most cases by experts.[78,79,144] Although raising target MAP from 65 to 85 mmHg in AMI-CS has been associated with CI improvement, and with lower lactate, and some better microcirculatory parameters,[145] a higher MAP target has not been associated with beneficial outcome in septic shock.[146] Expert recommendations thus do not consider higher MAP targets routinely necessary in CS.[78,79,147] An individual approach may, however, prove effective at least in those with a history of hypertension.[78,144] More importantly, correction of end-organ and tissue

perfusion is vital, as assessed by markers of systemic perfusion. Such markers include arterial lactate, UO, and mental status.[74] Markers of microcirculation include skin temperature, cyanosis, and mottling.

Intravenous positive inotropic agents are used to increase CO for correction of the hemodynamic disturbances and organ hypoperfusion resulting from compromised cardiac function. In turn, vasopressors are drugs used in hypotensive patients to increase blood pressure and redistribute blood to ensure adequate perfusion for vital organs. Most vasopressors have inotropic properties, whereas most inotropic agents are also vasodilators; thus, positive vasoactive medications can be categorized as inopressors and inodilators, as well. Many of the conventional inotropes and vasopressors are catecholamines acting through adrenergic receptors; the newer inodilators have distinct mechanisms of action.[148]

Whereas inotropes and vasopressors may be of benefit for hemodynamic stabilization, evidence, however, increases that their use–especially in patients without hypotension or organ hypoperfusion—may be harmful.[149-155] Catecholamines, in particular, may elevate myocardial oxygen and energy consumption, have cardiomyotoxic effects,[156] and provoke arrhythmias, due to their intense adrenergic stimulation;[148] AHF patients with concomitant ischemia or ACS may be particularly prone to adverse effects.[150,157]

2.5.3.1 Vasopressors

The vasopressors (i.e inopressors) most frequently used are dopamine, noradrenaline, and adrenaline. These are catecholamines acting through adrenergic α and β receptors. In cardiac myocytes, β_1-receptor stimulation causes an increased concentration of cyclic adenosine monophosphate in myocardial cells activating Ca^{2+} channels. This leads to Ca^{2+}-mediated chronotropy and positive inotropy by increasing the contractility of the actin-myosin-troponin system via increase in cytosolic Ca^{2+}. Stimulation of the α1-receptor promotes vasoconstriction, and β2-receptor stimulation causes peripheral vasodilation. These differential effects on adrenergic receptors from different catecholamines produce differing effects on blood pressure and flow. In addition, the total effect is a continuum, as most agents have a dose-dependent effect on differing receptors. Furthermore, reflexive autonomic changes after acute blood pressure alterations modify specific cardiovascular responses. In HF, for instance, desensitization and downregulation of adrenergic receptors may occur, and hypoxia and acidosis may also attenuate catecholamine effects.[158]

The main complications include excessive vasoconstriction, leading to peripheral and visceral hypoperfusion and ischemia. In addition, increased systemic vascular resistance and afterload may cause a decrease in stroke volume and oxygen delivery. Catecholamines can cause tachycardia and arrhythmias, and also cause myocardial ischemia by inducing coronary artery

vasoconstriction.[148,158] All catecholamines increase myocardial oxygen consumption through β_1-receptor stimulation.[159]

Noradrenaline is an α-adrenergic agonist with less pronounced β-adrenergic effects. It is a potent vasoconstrictor raising blood pressure but unlike pure vasoconstrictors, it does not cause deterioration of CO; it may, however, have a small positive effect possibly due to its β-adrenergic properties.[158] In addition, preload may be increased by a venoconstriction-mediated increase in venous return.[148,160]

Dopamine, the natural precursor of noradrenaline and adrenaline, shows dose-dependent pharmacological effects. Low, or dopaminergic, doses (<4 μg/kg/min) produce vasodilation in the coronary, renal, and mesenteric arteries, whereas ino- and chronotropy predominate at intermediate doses. The low-dose dopaminergic effects thought to preserve renal function and reduce risk for renal failure by increasing blood flow have, however, failed to translate into beneficial effects on outcome.[161,162] At higher doses, vasoconstrictive effects predominate, and thus dopamine has the propensity to raise afterload. Of note, a substantial overlap in these effects occurs, particularly in critically ill patients.[148]

Adrenaline is a potent inopressor elevating both CO and peripheral vascular tone. At low doses, β1- and β2-receptor effects predominate, whereas at higher doses, α1-adrenergic vasoconstrictive effects predominate.[158] It increases oxygen delivery, but myocardial oxygen consumption also rises.[163] In addition, lactate levels can rise,[164,165] possibly due to excess vasoconstriction, compromised perfusion, or increased lactate production; the relevance of lactatemia on outcome is, however, unclear. One main concern with adrenaline is its potential to reduce regional blood flow, especially in the splanchnic circulation.[166,167]

In addition to conventional catecholamines, there exist alternative vasopressors that are pure vasoconstrictors without ino- or chronotropic properties. ***Phenylephrine*** is a synthetic catecholamine selective for α_1-adrenergic receptors with a no effect on β-adrenergic receptors.[158] Although it can raise blood pressure in vasodilatory shock, concerns do arise as to its potential to reduce CO by increasing peripheral vascular resistance and afterload.[163] In addition, excess vasoconstriction may lead to peripheral and visceral hypoperfusion. ***Vasopressin***, in turn, by acting through V_1 receptors, constricts vascular smooth muscle cells and, through V_2 receptors, promotes water reabsorption by enhancing renal collecting duct permeability.[158] Addition of vasopressin, or its analogue ***terlipressin*** with its longer half-life, to catecholamines can raise blood pressure in pressor-refractory shock, and catecholamine requirements may decrease.[148] However, these properties have not translated into any beneficial effect on outcome,[168] and at high doses they may compromise splanchnic perfusion and may have independent deleterious effects on myocardial perfusion and CO.[169]

2.5.3.2 Inotropes

The main inotropes have differing mechanisms of action but produce somewhat the same effects: increase in myocardial contractility and vasodilation. However, differences exist in half-life and in effects, for example, on myocardial oxygen consumption.

Dobutamine, a synthetic catecholamine, has an agonist effect on β_1 and β_2 receptors, with a less pronounced effect on the α_1 receptor. The predominant effect is inotropic via β_1 stimulation resulting in increased heart rate and contractility.[158] Dobutamine may raise blood pressure by raising CO,[170] but the overall effect on blood pressure is variable due to counterbalancing effects of α_1-mediated vasoconstriction and β_2-mediated vasodilation. At higher infusion rates, vasoconstriction is predominant. Simultaneous β blockade dilutes the β-adrenergic properties of the drug.[171,172] Dobutamine significantly raises myocardial oxygen consumption,[159] even with mild chronotropic effects at low to medium doses, and may be particularly harmful in myocardial ischemia.[69] During infusion, tachycardia and ventricular arrhythmias can occur, and tolerance appears when infusion lasts over 72 h.[173] On the other hand, adverse effects are rapidly reversible, as the half-life is short, with the drug almost completely eliminated within 10-12 minutes after infusion cessation.[174]

Levosimendan is a calcium sensitizer, which, through calcium sensitization of contractile proteins in the cardiac myocytes, induces inotropy. It does not increase intracellular Ca_{2+} concentration and thus does not raise myocardial oxygen consumption.[175] In addition, it does not compromise diastolic relaxation and has a lucitropic effect.[176] Opening of mitochondrial ATP-sensitive potassium channels in smooth muscle cells results in vasodilation, and at higher doses, the drug also acts as a phosphodiesterase III (PDE3) inhibitor. The resulting pulmonary vasodilation may reduce pulmonary pressure and improve RV function. In CS, levosimendan, when added to noradrenaline and dobutamine, reduces pulmonary vascular resistance and improves RV function.[177] In addition, several other pleiotropic effects may occur, such as anti-inflammation, cardioprotection against ischemia, and preservation of renal function.[176] The clinical significance of these effects is, however, unclear. The main adverse effects of levosimendan include hypotension and tachycardia. Levosimendan has a long half-life (96 hours),[178] meaning the inotropic effect lasts for days.

Milrinone is a PDE3 inhibitor that raises intracellular cAMP and thus has inotropic effects independent of β receptors. Increased cAMP in vascular smooth muscle cells causes vasodilation resulting in reduction in systemic and pulmonary vascular resistance; it is often preferred in cases of predominant RV failure.[178] In addition, it improves diastolic relaxation.[174] The potential to increase myocardial oxygen consumption is one of the main concerns regarding its use, and it has been associated with worsened outcomes in patients with HF of ischemic origin.[150] In addition, it may cause hypotension and arrhythmias. Its half-time is relatively long (≥50 min).[174]

2.5.3.3 Current recommendations on use of vasopressors and inotropes

In CS, when vasopressor therapy is vital, the current drug of choice is noradrenaline.[28,78,79] In the ESC HF guidelines, dopamine has been and still is regarded as an alternative,[28,31,44,45] as in a recent ACC/AHA Scientific Statement on CS management,[74] whereas the current ESC STEMI guidelines cautiously recommend noradrenaline over dopamine.[63] Some expert and local guidelines do not recommend dopamine in CS.[78,179] Adrenaline has been restricted to resuscitation protocols and is considered an alternative in refractory cases in the ESC guidelines.[28] One recent expert recommendation, however, considers adrenaline an alternative to a noradrenaline-dobutamine combination.[78]

Dobutamine is the inotrope most recommended.[28,63,78] Comparative data between inotropes are, however, scarce, with the most recent Cochrane review on inotropes for AMI-CS finding no data to support any one inotropic drug as superior.[180] Meta-analyses have suggested, however, that in critically ill and patients with severe heart failure, levosimendan may be more beneficial than other inotropes.[181,182]

The randomized controlled SURVIVE trial compared the efficacy and safety of dobutamine and levosimendan in patients hospitalized for AHF.[183] No statistically significant difference appeared in mortality at 31 or at 180 days, but a subgroup analysis showed that short-term mortality was lower with levosimendan among patients with chronic HF and among those on β-blocker therapy.[183] Thus, levosimendan may prove beneficial in patients with myocardial ischemia and efficacious in those using or receiving β blockers. A recent subanalysis of the SURVIVE trial has suggested that the lower mortality observed with levosimendan than with dobutamine in the Finnish population when compared with mortality in other countries could have been related to the Finns' higher proportion of β-blocker users and MI.[184] In fact, European recommendations include levosimendan as the main alternative in hypoperfused patients and in those in shock, especially if they have STEMI[63] or are receiving β blockers.[28,78]

No direct comparison between levosimendan and milrinone has been carried out but levosimendan has appeared superior to another PDE3 inhibitor, enoximone, in refractory AMI-CS.[185]

2.5.3.4 Mechanical circulatory support

In addition to fluids and medical therapy in hemodynamic stabilization of patients with CS that is refractory to vasoactive medications, one must consider mechanical support to prevent or reverse multi-organ system dysfunction. The intra-aortic balloon pump (IABP) has been the device most extensively used with its rate ranging from 20 to 40% in AMI-CS patients,[20] and even up to 90% in those with refractory shock.[186] It improves diastolic

and lowers end systolic pressure without affecting mean blood pressure, but it does not improve relevant hemodynamic parameters such as CI.[187]

In the ESC 2012 guidelines,[188] the recommendation for IABP use was downgraded to class II based on a meta-analysis.[189] Furthermore, the recent randomized IABP-SHOCK II trial showed for benefit on short- or long-term outcome with IABP use in AMI-CS.[19,89] Consequently, current ESC guidelines do not recommend routine use of IABP,[28,63,138] although it should be considered for CS caused by mechanical complications such as acute mitral regurgitation or interventricular septal rupture.[63,138] Other mechanical devices include percutaneous LV assist devices and extra-corporeal life support (formerly called extracorporeal membrane oxygenation). However, no trial has shown any benefit for outcome thus far, and multiple open issues remain, such as optimal timing of device insertion and appropriate patient selection.[190] Still, ESC guidelines recommend consideration (class II recommendation) of mechanical circulatory support in refractory CS.[28,63,138]

2.6 ACUTE KIDNEY INJURY IN CARDIOGENIC SHOCK

2.6.1 DEFINITION AND CLASSIFICATION

"Acute kidney injury," replacing the term "acute renal failure," refers to a "clinical syndrome characterized by a rapid (hours to days) decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea and other clinically unmeasured waste products" with or without a decrease in urine output (UO).[191]

Kidney Disease: Improving Global Outcomes (KDIGO) defines and stages AKI are shown in Table 1.[192-194]

Table 1. *Acute kidney injury definitions and staging according to the KDIGO guidelines.*

Stage	Creatinine	Urine output
1	1.5-1.9 times baseline *or* ≥0.3mg/dl (26.5 µmol/l) increase	UO <0.5 ml/kg/h for ≥6 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	≥3 times baseline *or* increase to >4.0mg/dl (353 µmol/l) *or* initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 hours *or* anuria for ≥12 hours

UO = urine output

In HF, the concept adopted is “worsening renal function” (WRF). The current suggestion for the WRF definition in AHF is similar to the AKI definition in the KDIGO guidelines: an increase of 1.5–1.9 times baseline creatinine within 1–7 days before or during hospitalization *or* ≥ 26.5 mmol/L increase in creatinine within 48 hours *or* a UO < 0.5 mL/kg/h for 6–12 hours. A phenomenon called pseudo-WRF or pseudo-AKI has also been recently acknowledged in AHF, suggesting that some increase in creatinine is acceptable when the clinical status of a patient either improves or remains unaltered; thus it seems that pseudo-AKI does not translate into poor outcome.[41,195]

2.6.2 DIFFERENT BIOMARKERS IN DETECTION OF AKI

2.6.2.1 Creatinine

Creatinine is the measure most frequently used for renal function in clinical practice. Creatinine clearance and GFR can be estimated with different formulas, of which the Cockcroft-Gault formula and the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula are best known. Of these, CKD-EPI is the most recent and has better accuracy than its predecessors.[196,197]

Estimation of GFR with creatinine is reliable only in steady-state conditions. However, AKI, by definition, is not a steady-state condition, and estimated GFR (eGFR) cannot serve in its detection. In addition, creatinine has numerous pitfalls: it is a slow marker of changes in renal function as it takes time to accumulate, and its level has a non-linear relationship with GFR and is affected by factors such as age, diet, muscle mass, comorbidities, drugs, acute illness, and hemodilution due to fluid therapy and accumulation,[198] Despite the pitfalls, creatinine kinetics serve for AKI detection, and increases in its level have correlated with poor prognosis in numerous clinical contexts,[191,198,199] including MI[200,201] and AHF.[202]

2.6.2.2 Urine output

As UO criteria have not undergone extensive validation, they should serve as a starting point for further evaluation.[192] In fact, these criteria have been found to increase sensitivity in AKI detection, and UO <0.5 ml/kg/h for 6 hours is more frequent than with AKI_{crea}.[27,203] However, conflicting results exist as to whether the 6-hour UO threshold of <0.5 ml/kg/h is adequate for prognosis assessment. This threshold has been questioned, with a 6-hour UO threshold of <0.3 ml/kg/h for AKI proposed to perform better in mortality prediction.[204] No data exist on AKI in CS by UO criteria.

2.6.2.3 Cystatin C

Cystatin C has been more accurate than creatinine in estimation of GFR[205] and also may be valuable in AKI prediction and detection[206,207] as well as in outcome assessment.[208] In the critically ill, one retrospective multicenter study showed CysC-based AKI criteria to be more predictive of short-term outcomes than was KDIGO or its two predecessors.[209] Analyses from the FINN-AKVA study have shown that CysC is an independent predictor of outcome and is a useful marker for AKI and mortality detection also in AHF.[210] Further investigations have confirmed these findings and the utility of CysC in prediction of cardiovascular events.[211] No data exist as to the utility of a CysC-based AKI definition in CS, however.

2.6.3 EPIDEMIOLOGY

Few studies on AKI—using different creatinine cutoffs—have been conducted concerning CS. Furthermore, although kidney dysfunction in the form of oliguria is one of the CS diagnostic criteria, only one study has included UO in its AKI definition.[212] In these few heterogeneous studies, AKI incidence has been variable: from 33% to 60% (Table 2).[212-216]

Table 2. *Studies on acute kidney injury in cardiogenic shock.*

Study by	Design/setting	AKI definition	AKI incidence	Outcome
Koreny (n=118)	Retrospective single-center/ ACS	urine output <20 ml/h, *and* either sCr rise ≥0.5 mg/dL (44.2mmol/L) or >50% above baseline (during 24 h)	33%	↑ in-hospital mortality
Marenzi (n=97)	Prospective single-center/ STEMI – IABP + PCI	sCr rise >25% from baseline (during 72 h)	55%	↑ in-hospital mortality
Lauridsen (n=5079)	Retrospective, national registry/ AMI	AKI treated with RRT	13% (treated with RRT)	↑ five-year mortality
Fuernau (n=190)	Predefined single-center substudy of IABP-SHOCK II/ AMI	sCr rise 26.4 mmol/L or >50% above baseline on day 2 or 3, and/or need for RRT	46%	↑ one-year mortality
Abadeer (n=293)	Retrospective single-center/ Refractory CS - MCS	Modified KDIGO creatinine criteria (during 7 days)	60%	↑ one-year mortality (stage 3 AKI)

ACS = acute coronary syndrome, AKI = acute kidney injury, AMI = acute myocardial infarction, CS = cardiogenic shock, IABP = intra-aortic balloon pump, MCS = mechanical circulatory support, PCI = percutaneous coronary intervention, RRT = renal replacement therapy, sCr = serum creatinine

A recent meta-analysis reported the incidence of WRF (or AKI) in AHF to be on average 23%; the WRF definition, however, has varied considerably between studies.[202] In comparison, AKI can be detected in up to one in five hospitalized adult patients according to the KDIGO criteria,[217] and in up to over two in three critically ill patients, when assessing AKI by both creatinine and by UO criteria.[26,27] The recent large multicenter FINNAKI study revealed the prevalence of AKI to be 39% among intensive care unit (ICU) patients in Finland.[25] The recent AKI-EPI study in an unselected ICU population reported CS to be the fourth most common etiology for AKI (13%) after sepsis (41%), hypovolemia (34%), and drug-induced AKI (14%).[26]

Only one study has reported risk factors for AKI in CS: LVEF <40%, age >75 years, and mechanical ventilation.[213] In AHF, typical predictors for WRF/AKI are old age, hypertension, chronic kidney disease, diabetes, and diuretic use.[202] Similar findings have emerged in the critically ill, and additional risk factors are cardiovascular diseases (CAD and HF), exposure to nephrotoxins (contrast media, drug toxicity), anemia, and fluid overload.[198,218] The FINNAKI study reported as independent risk factors for AKI the following: chronic kidney disease, pre-ICU hypovolemia and pre-ICU use of diuretics.[25]

2.6.4 PATHOPHYSIOLOGY OF AKI IN AHF AND CS

The pathophysiology of AKI in CS in particular has not been under study, nor is it clear overall.[191] In AHF, renal hemodynamics are now considered the main determinants of renal function and WRF. The non-hemodynamic factors, such as activation of the RAAS, activation of the sympathetic nervous system, endothelial dysfunction, inflammation, and anemia, are considered to play a minor role.[41]

Renal blood flow and GFR are regulated through vasoconstriction and vasodilation of the afferent and efferent arterioles. Regulation is controlled by the RAAS and tubuloglomerular feedback system. In addition, renal blood flow is also dependent on CI. While GFR may be maintained despite a reduction in renal blood flow and CI, in the most severe HF with the greatest reduction in CI and in renal blood flow, the GFR becomes dependent on afferent arteriolar flow.[219]

Although CO is a major determinant of WRF in HF and in other cardiovascular diseases,[219-221] the role of venous congestion as another important determinant of GFR reduction has been increasingly stressed. A strong association, independent of any reduction in renal blood flow, exists between CVP, which reflects venous congestion, and GFR.[220,222] CVP has, in patients undergoing right heart catheterization due to cardiovascular diseases of various etiologies, a negative association with GFR and a positive correlation with increased mortality.[221] Such studies have not, however, been conducted in CS.

2.6.5 PROGNOSIS IN CS COMPLICATED BY AKI

The few studies on AKI complicating CS have reported AKI to associate with increased mortality both in the short[212,213] and long term (Table 2).[215,216] AKI treated with renal replacement therapy in CS has been shown to associate with poor long-term prognosis plus risk for chronic dialysis.[214] Likewise, AKI/WRF in AHF is associated with a significant increase in mortality[195] and risk for rehospitalization.[223] In comparison, 90-day mortality has also been significantly higher among Finnish ICU patients with AKI than in their non-AKI counterparts (33.7% vs 16.6%).[25] Although the association is known between AKI and mortality in AMI-CS, no such analyses exist in CS of various etiologies using the contemporary creatinine and UO definitions in the KDIGO guidelines.

3 AIMS OF THIS STUDY

The overall aim of this study was to assess the administration of pharmacotherapies and other guideline-recommended therapies in various clinical profiles of acute heart failure (AHF), with special focus on vasoactive medications. The last part of the study focused on acute kidney injury (AKI) in cardiogenic shock (CS). In more detail, the aims were:

1) To evaluate differences in clinical presentation, and especially in systolic blood pressure on admission, in relation to various forms of treatment in AHF. (I)
2) To compare AHF patients with and without concomitant acute coronary syndrome in relation to clinical profile, realization of treatment modalities, and short- and long-term survival. (II)
3) To analyze current real-life use of vasopressor and inotropic medications in CS, and to detect possible differences in outcomes, hemodynamic parameters, or safety profiles related to administration of these medications. (III)
4) To describe the incidence and outcome of AKI in CS by use of the contemporary creatinine and urine output definitions, to assess hemodynamic alterations associated with AKI, and to investigate the utility of cystatin C in the definition of AKI definition and outcome prediction. (IV)

4 SUBJECTS AND METHODS

4.1 STUDY POPULATIONS AND DATA COLLECTION

This is an observational study based on two prospective multicenter studies. Studies I-II were planned on the basis of the already available national FINN-AKVA study on AHF to describe use of AHF pharmacotherapies and their implementation in clinical practice in relation to guidelines. With special interest in vasoactive medication and the critically ill, Studies III-IV were a natural continuum in the study entity, and they were expected to be based on the then-on-going multinational CardShock study led and coordinated by the Heart Failure Study Group of Helsinki University Hospital. As different clinical profiles are essential in treatment guidance and prognostication, investigation of two poorly described clinical entities, one in AHF (ACS-AHF), and one in CS (AKI complicating CS), was considered necessary and thus planned in the study entity as well.

4.1.1 THE FINN-AKVA STUDY (I-II)

Data on the subjects of Studies I-II came from the observational multicenter FINN-AKVA study, which enrolled 620 consecutive patients hospitalized due to AHF from 14 hospitals in Finland during three months in 2004. Patients with *de novo* AHF and awCHF were included and enrolled only once during the study period. The FINN-AKVA study recruited patients with AHF symptoms, signs and diagnostic findings. AHF was classified on the basis of clinical presentation similarly to the ESC 2005 guideline:[44] 1) CS, 2) PO, 3) ADHF, 4) hypertensive AHF, and 5) right HF. Np patients with high output HF were included. The AHF diagnosis had to be confirmed during hospital stay. Local investigators assessed precipitating factors for AHF (ACS, infection, valvular disease, arrhythmias).

Local research fellows collected detailed data on patients' medical history, clinical presentation, and management. Documentation included length of hospital stay as well as admissions to cardiac (CCU) and intensive care units. All-cause mortality was determined for all patients up to five years after the index hospitalization from the national Population Register Centre (Väestörekisterikeskus), as was the time of death. All patients gave a written consent. The FINN-AKVA study was approved by the national ethics committee and was conducted in concordance with the Declaration of Helsinki.

A detailed description of the study population and associated mortality up to one year has appeared previously.[224] Briefly, mean age was 75 years, 49,5% were women, and 49% had *de novo* AHF, 51% awCHF. On admission, average SBP was 147 mmHg, diastolic blood pressure 82 mmHg, and heart

rate 91 bpm. Echocardiographic data were available in two-thirds of patients; mean LVEF was 45%. Among the laboratory biomarkers on admission, mean hemoglobin was 127 g/L and sodium 138 mmol/L whereas median creatinine was 98 μmol/l, troponin T (TnT) 0.01 μg/L and N-terminal pro-B-type natriuretic peptide (NT-proBNP) 5627 pg/ml. The median length of hospital stay was 7 days. Of the patients, 40% were admitted to a cardiac care unit and 12% to an ICU. Survival at 3 months was 85.0% and at one year 72.6%; one-year mortality was higher in awCHF than *de novo* AHF (33.5% vs 21.1%, p<0.001). An analysis of long-term outcome published by Lassus et al.[225] reported survival to be 39.5% at five years, and significantly worse in awCHF than in *de novo* AHF (44.7% vs 75.6%, p<0.001).

4.1.2 STUDIES I-II

Study I investigated use of AHF treatment modalities in various clinical profiles of AHF. Clinical profiling was based on clinical classification and on previous history of HF (*de novo* AHF vs awCHF).

Patients were also categorized according to admission SBP: <120 (low-normal), 120–160 (normal-high), and >160 mmHg (high). SBP cutoffs were based on clinical relevance and SBP categorization previously used in analyses on treatment use[226] and outcome.[8,36] In addition, each SBP had to have adequate number of patients. Patients with SBP <100 mmHg were few and thus included in the group SBP <120 mmHg for most analyses whereas the cutoff for truly hypertensive was set at 160 mmHg. Assessment of pharmacotherapy administration according to SBP groups was performed in the two largest clinical classes (ADHF and PE), and according to history of HF (de novo AHF and awCHF).

AHF treatment modalities were assessed as follows: furosemide, nitrates, and opioids (all intravenously administered) up to 12 hours, and vasopressors (dopamine, noradrenaline, adrenaline), inotropes (dobutamine, levosimendan), and NIV up to 48 hours from baseline. Independent predictors of therapy use were investigated from baseline patient characteristics.

Study II focused on describing the features and clinical significance of ACS-AHF. It further continued the investigation of pharmacotherapy in this context. Patients were categorized into two groups: ACS-AHF and nACS-AHF, for comparison in respect to patient characteristics, AHF management and prognosis. ACS was defined as unstable angina pectoris or AMI. AHF management was investigated similarly to Study I. In addition, utilization rates were assessed of invasive coronary procedures and prescription of evidence-based HF oral therapies (β blockers, ACEi/ARBs, mineralocorticoid receptor antagonists). Patient survival and mortality at 30 days, one year, and five years underwent analysis.

4.1.3 THE CARDSHOCK STUDY (III-IV)

Studies III-IV were based on The CardShock study (Clinicaltrials.gov identifier: NCT01374867) that prospectively enrolled 219 patients with CS at nine tertiary hospitals in eight European countries (Czech Republic, Denmark, Finland, Greece, Italy, Poland, Portugal, and Spain) between October 2010 and December 2012. In addition to a cardiac cause/etiology (e.g. ACS, mechanical complication of AMI, cardiomyopathy, myocarditis, valvular causes, awCHF), the inclusion criteria comprised SBP <90 mmHg (in the absence of hypovolemia or after adequate fluid challenge) for at least 30 minutes, *or* need of vasopressor therapy to maintain adequate perfusion pressure, *and* signs of hypoperfusion (any of the following: altered mental status/confusion, cold periphery, oliguria, blood lactate >2 mmol/l). Patients had to be over 18 and included within 6 hours of the identification of shock according to the inclusion criteria. Patients with CS after cardiac surgery or due to ongoing hemodynamically significant arrhythmia were excluded.

Detailed data were collected on demographics, medical history, and clinical, biochemical, and hemodynamic parameters. In addition, medical and invasive treatment procedures were registered. Hemodynamic measurements were performed at baseline (0 h), 6 h, 12 h, 24 h, 36 h, 48 h, 72 h and 96 h. CI and CVP measurements (at one or more time points) were available for 75 patients with pulmonary artery catheter, and an additional 68 patients had CVP measurements available from a central venous catheter. Serial blood samples were collected at 0 h, 12 h, 24 h, 48 h, 72 h, and 96 h. Creatinine, high-sensitivity troponin T (hsTnT), NT-proBNP and CysC were analyzed centrally.

Patients were treated according to local practice in each hospital. Vital status during follow-up was determined through direct contact with the patient or next of kin, or through population and hospital registries. The primary end-point in Studies III-IV was 90-day mortality; three patients were lost to follow-up. All patients or their next of kin gave informed consent.

The CardShock study was approved by local ethics committees at the participating centers apart from Copenhagen: according to Danish law (https://www.retsinformation.dk/forms/r0710.aspx?id=137674) scientific projects using only information from existing registries do not require approval from a scientific ethics committee. Thus, ethical approval and informed consent was not required from the Danish Ethics Committee as this study was conducted in a public organization using encrypted personal data; the study was approved by the Danish Protection Agency with reference number GEH-2014-013; I-Suite number: 02731. The CardShock study was conducted in accordance with the Declaration of Helsinki.

The study population, in-hospital mortality and its predictors, and differences between non-ACS and ACS patients were described in a recent publication.[227] In short, the etiology was ACS in most patients (81%), of which 84% had STEMI. Mechanical complications of MI were identified in 9%. The main non-ACS etiology was worsening of chronic HF, 11%, followed

by valvular and other mechanical causes, stress-induced cardiomyopathy (Takotsubo) and myocarditis. Compared with non-ACS patients, those with ACS were older at a mean age 68 [standard deviation (SD) 11] y vs 62 (SD 15) y, more often men (88% vs 57%) and had more often a history of diabetes (32% vs 14%). Non-ACS patients more frequently had a history of HF (48% vs 9%), renal insufficiency (26% vs 8%), or atrial fibrillation (36% vs 10%). The main differences in clinical presentation were evident: in ACS, initial confusion or altered mental status (71% vs 52%) was more frequent, and high-sensitivity TnT levels were higher and NT-proBNP levels lower. Otherwise, differences in patient characteristics were few. In-hospital mortality was 40% in ACS and 24% in non-ACS. An early prediction model for in-hospital mortality created from independent predictors of mortality was created and further refined with addition of eGFR as a variable. The final CardShock risk score consists of seven variables giving a maximum of nine points, as shown in Table 3. The score had a good performance in early prediction of in-hospital mortality: AUC 0.85 (95% CI 0.80–0.90), outperforming the APACHE II[228] with an AUC 0.76 (95% CI 0.67–0.84) and Sleeper score [88] with an AUC 0.76 (95% CI 0.69-0.83). The CardShock score was validated in the IABP-SHOCK II trial[19] population, in which it outperformed the Sleeper score.[88]

Table 3. *The CardShock risk score for prediction of in-hospital mortality.*

Variable	Score
Age >75 years	1
Confusion at presentation	1
Previous MI or CABG	1
ACS aetiology	1
LVEF <40%	1
Blood lactate	
<2 mmol/L	0
2-4 mmol/L	1
>4 mmol/L	2
$eGFR_{CKD\text{-}EPI}$	
>60 mL/min/1.73m²	0
30-60 mL/min/1.73m²	1
<30 mL/min/1.73m²	2
Maximum	*9*

ACS = acute coronary syndrome, CABG = coronary artery bypass graft surgery, $eGFR_{CKD\text{-}EPI}$= estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula, LVEF = left ventricular ejection fraction, MI= myocardial infarction.

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4.1.4 STUDIES III-IV

Study III was an observational substudy that continued investigating use of vasoactive medications, focusing on vasopressors and inotropes in CS, the most severe form of AHF. This study sought to detect possible differences in safety profiles of vasopressor and inotropic medications, in terms of mortality as well as cardiac and renal injury.

The medications were categorized as in studies I-II: noradrenaline, adrenaline, and dopamine as vasopressors, whereas dobutamine and levosimendan as inotropes. In addition, vasopressin and terlipressin were considered vasopressors, whereas PDE3 inhibitors (milrinone or enoximone) were considered inotropes. Vasoactive medications were registered and analyzed up to 96 hours from the study baseline including information on infusion duration and maximum infusion rate. To evaluate differences in cardiac and renal injury between vasoactive groups, evolution of high-sensitivity TnT, and NT-proBNP, and creatinine levels were analyzed over time. Similarly, to evaluate hemodynamic stabilization, evolution of hemodynamic parameters (MAP, heart rate and CI) was assessed up to 96 hours from baseline.

Study IV investigated the characteristics and significance of the clinical entity of CS complicated by AKI. The study was designed to detect differences among AKI definitions with respect to AKI incidence and to assess their utility in prognostication. Furthermore, the study was planned to describe AKI-related hemodynamic alterations.

AKI was defined and staged as in the KDIGO guidelines by creatinine (AKI_{crea}) and UO (AKI_{UO}) criteria. UO was measured in 6-hour intervals until 24 hours from baseline, and consecutive 6-hour intervals were evaluated for AKI_{UO} staging. In addition, CysC served to define and stage AKI similarly as was AKI_{crea}: ≥0.3 mg/L or ≥50% increase from baseline as stage 1, 100–199% increase as stage 2, and ≥200% increase as stage 3 AKI_{CysC}.[118,207,209,210] Assessment of AKI_{crea} and AKI_{CysC} was based on creatinine and CysC levels in serial plasma sampling from baseline until 48 hours, and the highest increase within this time was used for staging. AKI staging included no renal replacement therapy, unless stated otherwise. Hemodynamic parameters were analyzed over time similarly as in Study III.

The patient populations Studies III and IV are in the flow chart (Figure 3).

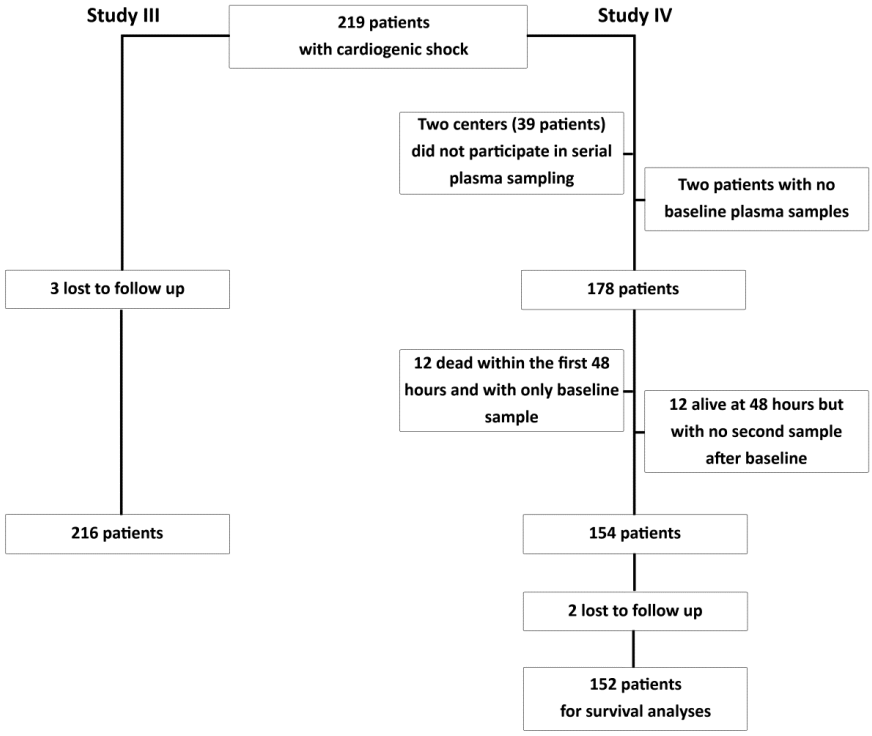

Figure 3 Flow chart of patients included in Studies III-IV.

4.2 STATISTICAL ANALYSES

Group comparisons were performed with Fisher's exact or chi-square test for categorical variables, the Mantel-Haenszel trend test for ordinal, and the t-test or Mann-Whitney U-test for continuous variables, as appropriate. Results are presented as percentages, means with standard deviation or medians with interquartile range. Linear mixed modeling allowed assessment of differences in biomarkers and hemodynamic measurements between groups over time (III-IV). For these analyses, biomarkers were log-transformed to normalize the distribution and the residuals, whereas mean values for hemodynamic measurements were calculated at time points 0–12 h, 18–24 h, 36–48 h, and 72–96 h.

Multivariable logistic regression served to identify independent determinants of AHF therapies (I) and to assess independent predictors of mortality (II-IV). Goodness-of-fit of a model was subject to the Hosmer-

Lemeshow test. Unadjusted survival was analyzed by the Kaplan-Meier method and compared between groups by the log rank test. Multivariable Cox regression served in adjusted survival analyses (III-IV); the assumption of proportional hazards was checked with parallelism of log-log survival curves. The additive value of a variable in mortality prediction was assessed via the likelihood ratio test for nested models (IV). Discriminative capability was assessed by the area under the receiver operating curve (AUC) (IV). AUC comparisons were performed with DeLong method (IV).

Study III included propensity score adjustment and matching to reduce bias and residual confounding when assessing the effect of a treatment on mortality.[229] The propensity score was estimated with potential confounders of outcome;[230] the variables were chosen based on clinical relevance and knowledge based on association with outcome. However, as the sample size was limited, priority in choosing variables went to those believed or observed to be related to outcome instead of those mainly associated with treatment assignment,[231] while retaining an acceptable balance between groups after propensity score matching. The score was estimated with multivariable logistic regression with treatment variable as the outcome and covariates as the predictor variables in the model.[230] The score estimate was converted into a logit scale for propensity score adjustment, and then used as a covariate in logistic and Cox regression.

Propensity score matching was used in a subgroup and sensitivity analysis to confirm the effect of adrenaline on mortality. To maximize the number of patients ((i.e. not to exclude patients because of a missing covariate value) in the matching procedure, patients with missing data were included by means of the multiple imputation method. The matching was performed using a 1:1 nearest neighbor matching without replacement with a caliper <0.2 of the standard deviation of the logits of the propensity scores. Balance was assessed by the standardized mean differences (SMD) in the propensity scores, the covariates used, and the average of absolute SMDs of covariates. SMD is the difference in means of each covariate, divided by the SD in the full treated group; the same standard deviation was used in the standardization before and after matching. Balance was considered good with SMD <0.1.[231]

The CardShock risk score as a continuous variable was used for adjusted mortality analyses in Study IV.

P-values <0.05 were considered statistically significant. Statistical analyses were performed with PASW Statistics, Version 18.0 (SPSS Inc, Chicago, IL, USA), IBM SPSS Statistics, Versions 21.0-24.0 (IBM Corp, Armonk, NY, USA), and MedCalc Statistical Software, Versions 17.1-17.5 (MedCalc Software bvba, Ostend, Belgium). Additionally, IBM SPSS Statistics Essentials for R and SPSS PS Matching plugin were used for propensity score matching. A Venn diagram was drawn with eulerAPE.

5 RESULTS

5.1 PROGNOSIS AND MANAGEMENT ACCORDING TO AHF CLINICAL PRESENTATION (I)

5.1.1 CLINICAL CLASSIFICATION AND PROGNOSIS

The FINN-AKVA study included a total of 620 patients, mean age 75 years; half were women. The most common precipitating factor for AHF was ACS (32%), followed by atrial fibrillation/flutter (29%), infection (24%), and valvular disease (12%).

ADHF was the most common clinical manifestation (63.5%), while 26.3% of patients had PE, 2.3% CS, 3.1% hypertensive HF, and 4.8% right heart failure. Differences between *de novo* AHF and worsening of CHF have been described.[224] In-hospital mortality was 7.1% overall and 9.4% at 30 days. Short-term mortality was lowest in hypertensive and right HF and highest in CS. However, long-term mortality was poor, irrespective of clinical class (Table 4).

Table 4. *Short- and long-term mortality according to clinical classification of AHF.*

Charasteristic	Total	ADHF	PE	Right HF	Hypert. HF	CS	p
n	620	394	163	30	19	14	
Mortality (%)							
In-hospital	7.1	6.1	9.8	0	0	28.6	0.007
30-day	9.4	8.1	12.3	3.3	5.3	28.6	0.040
1-year	27.6	24.9	31.9	43.3	15.8	35.7	0.073
5-year	60.5	58.1	65.6	66.7	57.9	57.1	0.5

ADHF = acute decompensated heart failure, CS = cardiogenic shock, HF = heart failure, PE = pulmonary edema. p = p value for comparison of mortality between groups

5.1.2 CLINICAL CLASSIFICATION AND AHF MANAGEMENT

Use of recommended AHF therapies is outlined in Table 5. IV furosemide was the most commonly administered therapy, one received by more than two-thirds of patients in all clinical classes within the first 12 h, even in CS. The second most common treatment was IV nitrate, the third was IV opioids. Use of NIV was most common for PE, while inotropes and vasopressors were mainly given for CS but also somewhat often for PE, as well. Inotropes and vasopressors were initiated within the first 24 hours in a majority of patients (27/33, 82%, and 40/46, 87%, respectively).

Table 5. *AHF-therapy use according to clinical class in percentages.*

Treatment	All	ADHF	PE	Right HF	HTHF	CS	p
Furosemide	76	69	93	77	74	71	<0.001
Nitrate	42	32	68	13	58	43	<0.001
Opioid	29	20	54	10	26	43	<0.001
Inotrope	5	2	10	0	0	57	<0.001
Vasopressor	7	4	13	0	0	71	<0.001
NIV	24	12	55	0	32	57	<0.001

ADHF = acute decompensated heart failure, CS = cardiogenic shock, HF = heart failure, HTHF = hypertensive HF, PE = pulmonary edema. p = p value for comparison of treatment use between groups.

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With regards to *de novo* AHF and awCHF, opioids (34 vs 24%) and vasopressors (10 vs 5%) had been more frequent for the latter group (34% vs 24% and 10% vs 5%, respectively) but furosemide less often (72% vs 79%). Use of nitrates, inotropes, or NIV did not significantly differ between groups.

5.1.3 SBP AND PROGNOSIS

Figure 4 shows a comparison of survival between the SBP groups (<120 mmHg, 120-160 mmHg and > 160 mmHg). Mortality at 30 days, one year (365 days), and five years (1825 days) was highest among patients with SBP <120 mmHg (Figure 4; log rank $p<0.05$ for all pairwise comparisons with SBP <120 mmHg); these associations remained independent after multivariable adjustment.

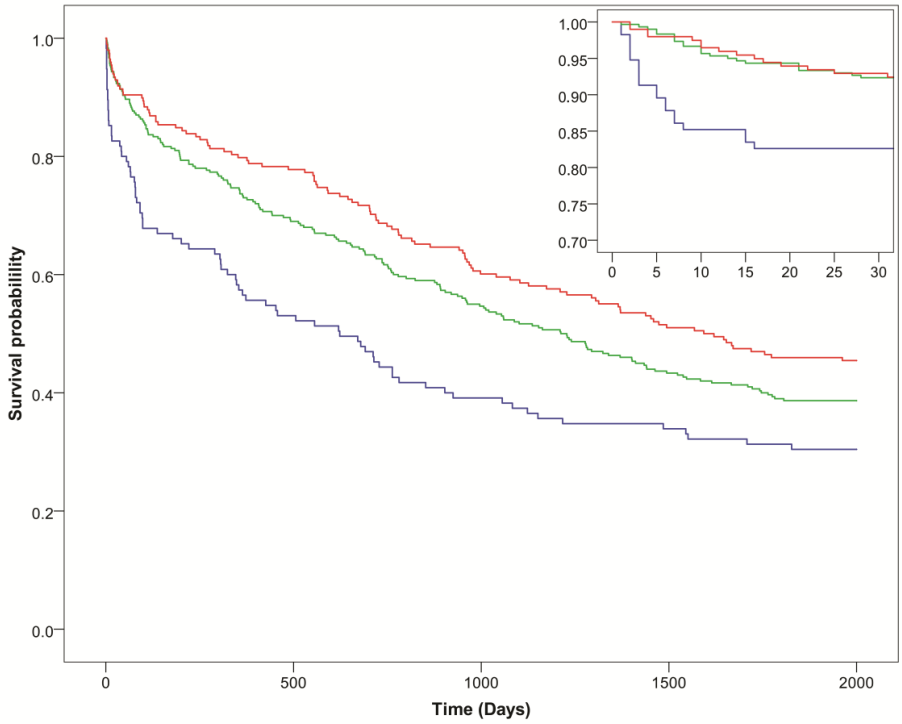


Figure 4 Kaplan-Meier survival curves according to systolic blood pressure (SBP) on admission. The inset figure represents difference in 30-day survival. Blue line = SBP <120 mmHg, green = SBP 120-160 mmHg, and red = SBP >160 mmHg.

5.1.4 SBP AND AHF MANAGEMENT

SBP was related to use of all AHF therapies apart from furosemide; the correlation was negative for inotrope and vasopressor therapies but positive for nitrates, opioids, and NIV. Even with CS, right HF, and hypertensive AHF excluded, associations between SBP and AHF therapies remained. Nitrate administration was uncommon in ADHF even with SBP >160 mmHg, whereas more than half the PE patients with SBP <120 mmHg were treated with nitrates (Figure 5). In contrast, among PE patients, mean SBP on admission was as high as 130 mmHg (SD 26) for inotropes and 134 mmHg (SD 37) for vasopressors.

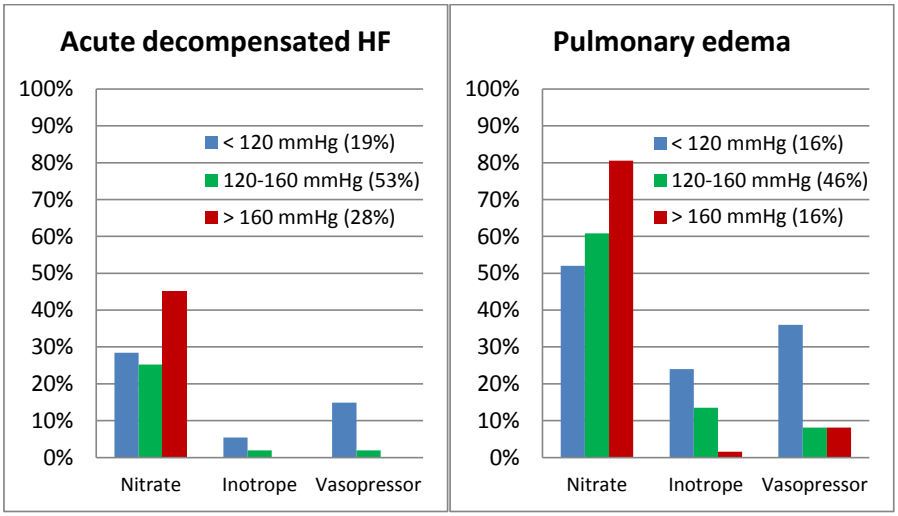


Figure 5 Administration of vasoactive medications in relation to SBP in ADHF and PE. Patient proportions for each SBP group are shown in brackets. Data presented in more detail Study I; adapted and reproduced with permission of SAGE publications.

Even with CS patients excluded, nitrates, vasopressors, and inotropes were administered more than twice as often for *de novo* AHF than for awCHF when SBP was <120 mmHg. Notably, nitrates were still used twice as often in *de novo* AHF when SBP was <100 mmHg, but inotropes and vasopressors twice as often when SBP was 100-119 mmHg (Figure 6).

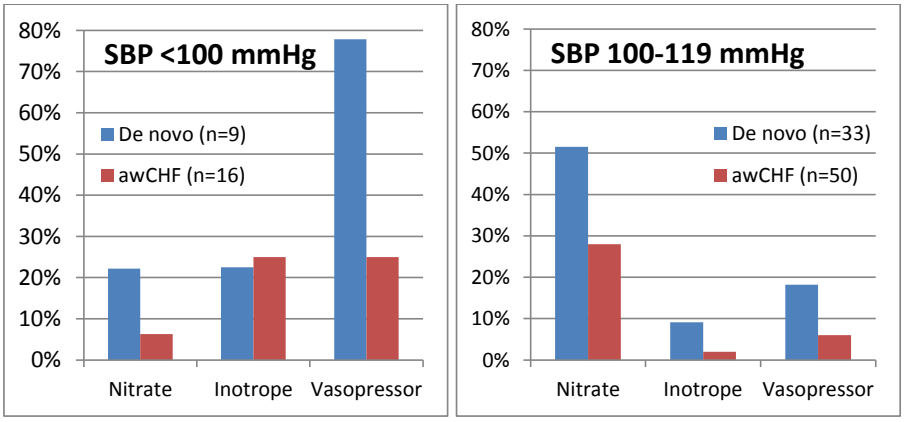


Figure 6 Comparison of administration of vasoactive medications between *de novo* AHF and awCHF in SBP groups <100 mmHg and 100-119 mmHg. CS patients are excluded.

Apart from furosemide, SBP on admission was independently associated with use of all AHF therapies. In addition, ACS and pneumonia were also independent predictors of AHF therapies.

5.2 ACUTE HEART FAILURE WITH AND WITHOUT CONCOMITANT ACUTE CORONARY SYNDROME (II)

5.2.1 PATIENT CHARACTERISTICS

Among AHF patients in the FINN-AKVA study population, ACS was a precipitating factor for 32%, and most ACS-AHF patients presented with *de novo* AHF (61%). Compared with those with nACS-AHF, they more frequently had a history of CAD (70% vs 48%), MI (39% vs 22%), and diabetes mellitus (40% vs 29%), but less often atrial fibrillation/flutter (13% vs 34%); the clinical class of AHF was more often CS (5% vs 1%) or PE (42% vs 19%). No significant differences emerged regarding biochemistry, apart from elevated TnT levels (≥0.03 μg/L) on admission (72% vs 29%, $p<0.001$) and at 48h (82% vs 26%, $p<0.001$).

5.2.2 PHARMACOTHERAPIES AND INVASIVE CORONARY PROCEDURES

All treatment modalities were significantly more frequent in ACS-AHF, and ACS was an independent predictor for all AHF therapies. The largest differences appeared in use of nitrates (69% vs 29%), of inotropes (11% vs 3%) and of vasopressors (10% vs 1%).

ACS-AHF patients underwent invasive coronary procedures during hospitalization more often than those with nACS-AHF, but rates were still low: coronary angiography in 35% vs 8%, PCI 16% vs 0.2%, and CABG 10% vs 1% ($p<0.001$ for all). Of those with no diagnosis of concomitant ACS, despite a significant proportion's having elevated TnT levels, only a minority (8%) were investigated with coronary angiography.

5.2.3 PRESCRIPTION OF CARDIOVASCULAR MEDICATIONS

Before hospitalization, furosemide, spironolactone, and warfarin were significantly more often used among nACS-AHF patients, but lipid lowering agents (most often statins), acetosalicylic acid, and clopidogrel were more common in ACS-AHF. These differences remained at discharge. In contrast, no difference appeared between the two groups on admission or at discharge with regard to use of β blockers or of ACEi/ARBs. Furthermore, no difference emerged in the discharge dosages of β blockers, ACEi/ARBs, or spironolactone in relation to their target doses. Prescription of cardiac medications increased, however, from admission to discharge.

5.2.4 ACS AND MORTALITY

In-hospital and 30-day mortality were higher in ACS-AHF (11.6% vs 5.0%; p=0.002, and 13.1% vs 7.6%, p=0.027). However, 1-year and 5-year mortality were similar (29.3% vs 26.8% and 59.1% vs 61.1%). Kaplan-Meier survival curves (30-day log rank p=0.024) are shown in Figure 7.

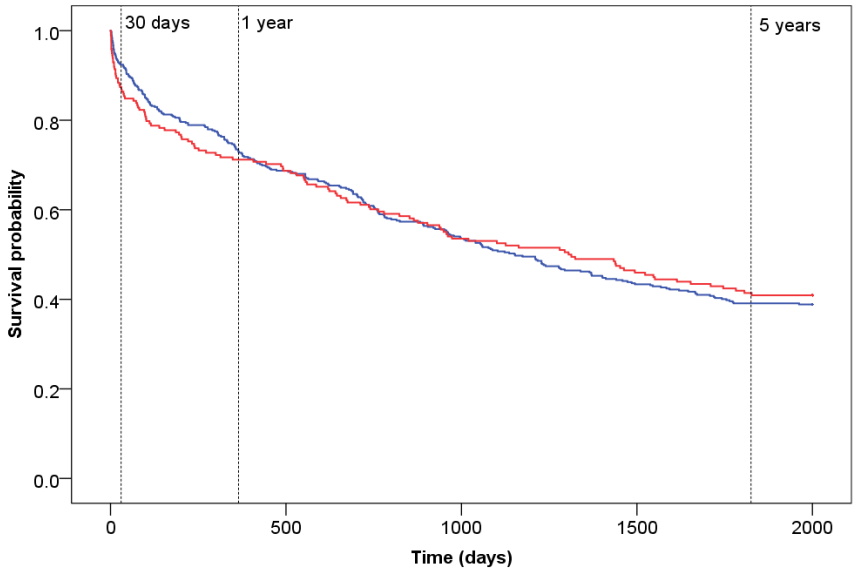


Figure 7 Kaplan-Meier survival curves in nACS-AHF (blue) and ACS-AHF (red). 30-day, 1-year and 5-years timepoints are shown by dashed vertical lines. Modified and reproduced from Study II with permission of Elsevier.

The unadjusted OR for 30-day mortality for ACS was 1.84 (95% CI 1.07-3.19, p=0.029). After adjustment by sex, age, medical history (CAD, HF, hypertension, chronic obstructive pulmonary disease and cerebrovascular disease), SBP on admission, anemia (defined as hemoglobin <120 g/L for women, <130 g/L for men), hyponatremia (sodium <135 mmol/L), and eGFR (calculated by CKD-EPI equation), the effect was retained with an OR of 1.98 (95% CI 1.05-3.72, p=0.035). The independent association was further confirmed by excluding separately patients admitted to ICU, those with CS, and unstable angina pectoris patients (to test the effect of actual MI on outcome); in all of these analyses, the result remained similar.

As patients with awCHF had significantly poorer long-term survival than those with *de novo* AHF[225] (and most ACS-AHF patients had *de novo* AHF), this study further tested whether the effect of ACS on outcome differed between these two groups. In the subgroup of *de novo* AHF, ACS seemed to associate with poorer survival (figure 8) but with only borderline significance (p for interaction 0.051).

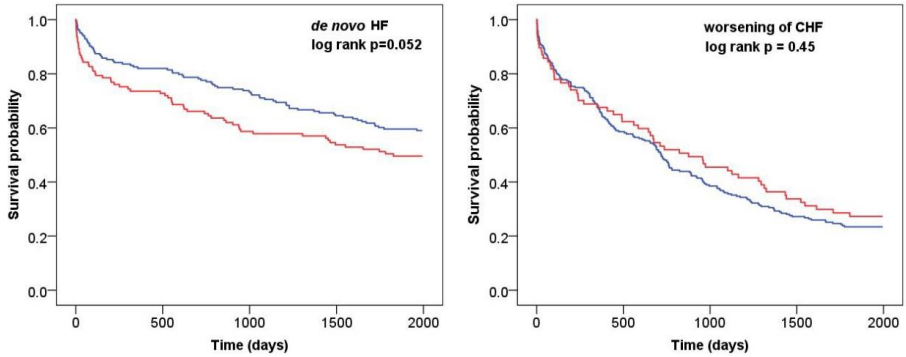


Figure 8 Kaplan-Meier survival curves for nACS-AHF (blue) and ACS-AHF (red) in *de novo AHF* (upper figure) and awCHF (lower figure). Previously unpublished.

5.3 VASOPRESSORS AND INOTROPES IN CARDIOGENIC SHOCK (III)

5.3.1 STUDY POPULATION

Study III comprised 216 CS patients from the CardShock study population. The 90-day mortality was 42%. Those dead by 90 days were older, more often had comorbidities (CAD, and history of MI, CABG, diabetes, and renal insufficiency), lower blood pressure, lower LVEF, more often signs of hypoperfusion on admission, were more often resuscitated from cardiac arrest prior to enrollment, and had worse biochemistry profiles on admission (higher creatinine, lactate, high-sensitivity TnT and NT-proBNP levels).

5.3.2 USE OF VASOACTIVE MEDICATIONS AND MORTALITY

Vasopressors and inotropes were administered (by infusion) to 94% of patients, and these were almost invariably initiated within the first 24 hours (vasopressors in 98% and inotropes in 94% of patients). Noradrenaline and dobutamine were the most commonly used vasoactives (Table 6). A fair proportion of patients receiving adrenaline (39%) were resuscitated from cardiac arrest prior to inclusion. Around half the patients (55%) received vasopressor-inotrope combinations, most often noradrenaline-dobutamine. A large proportion (29%) received vasopressors without inotropes, and 10% received only inotropes.

In unadjusted analyses, associated with 90-day mortality were noradrenaline, adrenaline, vasopressin/terlipressin, a vasopressor combination, and the combination of dobutamine with vasopressor(s), but not levosimendan with vasopressor(s) (Table 6).

Table 6. *Use of vasoactive medications and their association with 90-day mortality.*

	Overall use n (%)	90-day mortality (%):			Unadjusted OR (95% CI)
		With	Without	p	
Vasopressors					
Noradrenaline	162 (75)	47	24	0.003	2.8 (1.4-5.6)
Adrenaline	46 (21)	74	32	<0.001	5.9 (2.8-12.3)
Dopamine	56 (26)	43	41	0.8	1.1 (0.6-2.0)
Vasopressin/ terlipressin	8 (4)	88	39	0.01	10.8 (1.3-89.0)
Inotropes					
Dobutamine	105 (49)	48	35	0.06	1.7 (1.0-2.9)
Levosimendan	52 (24)	33	44	0.15	0.6 (0.3-1.2)
PDE3i	9 (4)	33	42	0.6	0.7 (0.2-2.9)
Combinations					
Vasopressor combination	65 (30)	66	30	<0.001	4.5 (2.4-8.3)
Dobutamine and vasopressor(s)	84 (39)	57	31	<0.001	3.0 (1.7-5.2)
Dobutamine-noradrenaline	81 (38)	58	31	<0.001	3.0 (1.7-5.4)
Levosimendan and vasopressor(s)	47 (21)	34 %	44 %	0.3	0.6 (0.3-1.2)
Levosimendan-noradrenaline	47 (21)	34%	44%	0.3	0.6 (0.3-1.2)

PDE3i = phosphodiesterase 3 inhibitor (milrinone or enoximone)

5.3.2.1 Adrenaline and mortality

Patients treated with adrenaline presented with a worse initial clinical profile: they significantly more often showed signs of hypoperfusion (confusion or altered mental status, oliguria, higher lactate levels) and worse renal function (higher creatinine level, lower eGFR). Differences in other clinical characteristics also occurred, pointing toward a worse initial presentation, but these did not reach statistical significance. Patients receiving adrenaline were more often treated during the study by intra-aortic balloon pump (74% vs 51%, p=0.005) and either a left ventricular assist device or extracorporeal membrane oxygenation (15% vs 2%, p=0.002).

Despite the differences between patients treated and not treated with adrenaline, multivariable analyses showed that adrenaline, alone, was independently associated with increased 90-day mortality. To reduce bias and promote precision, propensity score adjustment was used. Then logistic regression analysis adjusting for the propensity score allowed determination of the independence of the association between adrenaline and mortality: OR for 90-day mortality was 3.3 (95 % CI 1.4-7.7, p = 0.006), and HR was 2.0 (95% CI 1.2-3.4, p=0.008). After further adjustment for prior resuscitation from cardiac arrest, baseline renal function, and use of mechanical circulatory support (intra-aortic balloon pump, left ventricular assist device or extracorporeal membrane oxygenation), results remained similar.

The association between adrenaline and increased mortality remained similar, as well, when the analysis was repeated in the subgroup of patients treated with vasopressors (with or without inotropes): propensity-score-adjusted HR 1.9 (95% CI 1.1-1.3) for adrenaline compared with other vasopressors. The result remained similar when patients treated with a left ventricular assist device or with extracorporeal membrane oxygenation were excluded.

An additional sensitivity analysis with propensity score matching was performed. Matching in three imputed cohorts produced a pool of 40 matched pairs. The balance between the matched groups was good: the SMDs were <0.1. Adrenaline was still associated with high mortality: the pooled HR was 1.89 (95% CI 1.04-3.43, p=0.036) and OR 2.80 (95% CI, 1.10-7.14, p=0.031) for 90-day mortality.

5.3.2.2 Vasopressor-inotrope combinations and mortality

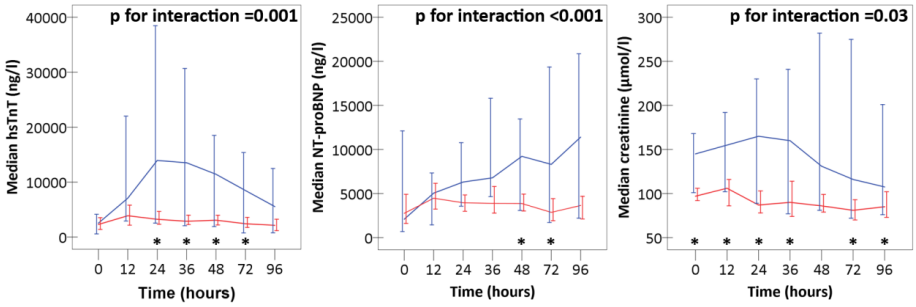
Vasopressor-inotrope combinations—noradrenaline-levosimendan in particular—were associated with better outcome than adrenaline. Therefore, the two most common vasopressor-inotrope combinations, i.e. noradrenaline-dobutamine and noradrenaline-levosimendan, were compared in relation to 90-day mortality; no difference appeared in propensity-score-adjusted analyses. The result remained similar when further adjusted with the maximum infusion rate of noradrenaline.

5.3.3 ADRENALINE AND ORGAN INJURY

To assess potential mechanisms by which adrenaline is associated with or affects mortality, Study III compared the evolution of hemodynamic parameters, and cardiac and renal biomarkers in adrenaline and in other-vasopressor groups. CI and MAP appeared to reach similar levels in both groups by time, and heart rate stabilized somewhat similarly. The evolution of hsTnT, NT-proBNP, and creatinine differed, however (Figure 9; $p<0.05$ for all time-by-group interactions). The kinetics of hsTnT and NT-proBNP in particular differed between the two groups. In addition, the overall levels of hsTnT and creatinine were significantly higher over time until 96 hours from baseline ($p<0.05$), whereas the overall level of NT-proBNP was no higher ($p=0.087$). The results remained similar despite adjustment for prior resuscitation from cardiac arrest.

Of note, no significant differences between noradrenaline-dobutamine and noradrenaline-levosimendan existed with regards to evolution of hemodynamic parameters or of TnT, NT-proBNP, or creatinine levels.

Figure 9 Evolution of TnT, NT-proBNP and creatinine levels over time in patients receiving adrenaline (blue) or other vasopressor(s) (red).



* $p<0.05$ for each between-group comparison at a time point

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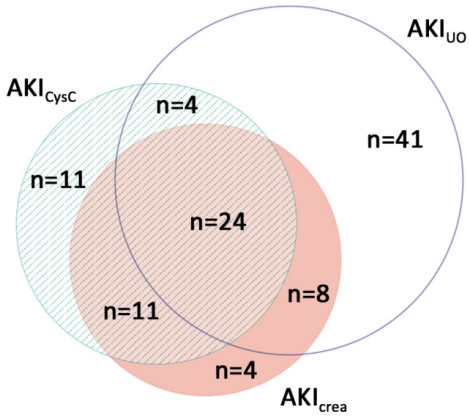
5.4 ACUTE KIDNEY INJURY IN CARDIOGENIC SHOCK (IV)

5.4.1 INCIDENCE OF AKI

At baseline, median creatinine was 104 (78-140) µmol/l, eGFR 64 (43-87) mL/min/1.73m², and CysC 1.19 (0.90-1.48) mg/l. Based on the KDIGO criteria, 31% developed AKI_{crea} and 50% AKI_{UO}, and AKI_{CysC} was observable in 33%. In patients who developed AKI_{crea}, 74% fulfilled those criteria during the first 24 hours and 26% (12/47) between 24 to 48 hours from baseline. Discordance appeared in the AKI definitions (Figure 10); over half the patients with AKI_{UO} developed neither AKI_{crea} (58%) nor AKI_{CysC} (64%). Notable differences emerged in distribution of AKI stages between the definitions (figure 10).



	Incidence of AKI stages		
Definition	**Stage 1**	**Stage 2**	**Stage 3**
Creatinine	18%	6%	6%
Urine output	22%	22%	7%
Cystatin C	26%	5%	2%

Figure 10 Proportions of AKI stages according to differing definitions. Venn diagram adapted and reproduced from Study IV with permission of Wiley.

Characteristics of patients with and without AKI were generally similar. AKI patients more often had a history of renal insufficiency and worse renal function (higher creatinine and CysC, and lower eGFR). Numerically, AKI_{crea} patients had used diuretics more often, but the difference was not statistically significant (p=0.06). Some differences arose in biochemistry and treatment modalities between AKI and non-AKI groups. AKI patients had higher lactate levels, and lower arterial pH at baseline. Among patients who underwent coronary angiography (83%), contrast volume was higher in $AKI_{crea/CysC}$ than in patients without AKI. In addition, IV furosemide was used more often in AKI_{crea} (81% vs 53%, p=0.003) and its cumulative dose within

the first 24 hours was higher in patients with AKI_{CysC} than in those without AKI [120 (IQR 60-210) mg vs 80 (23-178) mg, p=0.021].

Independent predictors for AKI_{crea} included lower baseline arterial pH and previous use of diuretics, whereas lower baseline eGFR was an independent predictor of AKI_{UO}. IV furosemide during the first 24 hours was independently associated with higher incidence of AKI_{crea} but not of AKI_{UO}. Previous prescription of ACEi/ARB was not associated with increased incidence of either AKI definition. Among those who underwent coronary angiography within 72 hours before and 24 hours after baseline, amount of contrast media volume was positively associated with AKI_{UO}, but not with AKI_{crea}. Of note, dopamine within the first 24 hours showed no correlation with AKI incidence.

5.4.2 CREATININE-BASED AKI AND MORTALITY

Compared with patients alive at 90 days, those who died had had higher creatinine: 114 (86-161) vs 92 (69-120) μmol/l, p=0.001, and lower eGFR; 51 (33-71) vs 71 (53-96) mL/min/1.73m2, p<0.001 at baseline; the odds ratio (OR) for death at 90 days was 1.07 (95% confidence interval (CI) 1.01-1.12) per 10 umol/l increase for creatinine, and 1.03 (95% CI 1.01-1.04) per mL/min/1.73m2 decrease in eGFR.

AKI_{crea} (Table 7) and all its stages were independently associated with increased 90-day mortality; when renal replacement therapy was included as a stage 3 AKI criterion, these results did not markedly change.

5.4.3 URINE OUTPUT AND MORTALITY

AKI_{UO} stages 2 and 3 were associated with increased rates of death, but stage 1 AKI_{UO} was not. Furthermore, AKI_{UO} overall failed to be an independent predictor of 90-day mortality, but stage 2 AKI_{UO} succeeded.

A stricter cutoff of <0.3 mL/kg/h for average 6-hour UO ($UO_{0.3}$), when explored and showed better discriminative capability for 90-day mortality than did <0.5 mL/kg/h, at AUC 0.589 (95% CI 0.506-0.668) vs 0.664 (95% CI 0.583-0.739, p=0.014 for AUC comparison. Combining $UO_{0.3}$ with AKI_{crea} improved 90-day mortality prediction compared with AKI_{crea} alone (p<0.001 for comparison of nested models) and was useful in stratifying patients according to mortality risk (when divided into four groups according to presence of AKI_{crea} and of $UO_{0.3}$). This threshold remained an independent predictor of mortality in multivariable adjustment. Table 7 shows unadjusted and adjusted associations of AKI_{crea}, AKI_{UO} stages 1 and ≥2, and $UO_{0.3}$ with 90-day mortality.

Table 7. *Associations between different AKI definitions and 90-day mortality.*

	AKI_{crea}	stage 1 AKI_{UO}	stage ≥2 AKI_{UO}	$UO_{0.3}$
Model	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Unadjusted	7.5 (3.5-12.3)	2.1 (1.05-4.0)	3.5 (1.7-7.4)	4.7 (2.2-9.8)
Adjusted	12.2 (4.1-36.0)	1.5 (0.6-3.5)	2.9 (1.2-7.2)	3.6 (1.4-9.3)

Variables in adjusted model: gender, SBP, CardShock risk score (see Subjects and Methods)

5.4.4 HEMODYNAMIC DERANGEMENTS

Development of AKI was associated with persistently elevated CVP and decreased CI and MAP (Figure 11; p<0.5 for all pooled between-group comparisons). This association was stronger in AKIcrea stage ≥2 than in stage 1, and in $UO_{0.3}$ than in UO 0.3-0.5 ml/kg/h for average 6-hour UO.

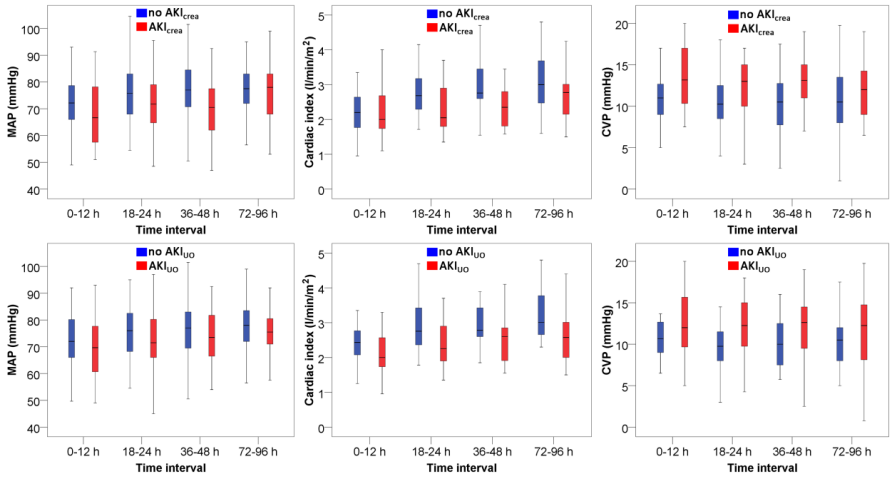


Figure 11 Evolution of hemodynamic alterations over time in AKI_{crea} (upper panel) and AKI_{UO} (lower panel).

5.4.5 UTILITY OF CYSTATIN C-BASED AKI DEFINITIONS

Those dead at 90 days had higher baseline CysC levels than did those still alive, at 1.39 (1.04-1.96) vs 1.13 (0.81-1.53) mg/L, p=0.001. A slightly greater proportion of patients had already developed AKI within the first 24 hours based on CysC than on creatinine criteria: 39/50, (78%) vs 35/47 (74%).

Increasing AKI_{CysC} stage was associated with a stepwise increase in mortality rates. AKI_{CysC} was an independent predictor of increased 90-day mortality (after adjustment for gender, SBP, and CardShock risk score): OR 2.5 (95% CI 1.0-6.1, p=0.04). Whereas AKI_{crea} without concomitant AKI_{CysC} was associated with increased 90-day mortality (67% vs 24%, p=0.002), AKI_{CysC} without concomitant AKI_{crea} was not (21% vs 29%, p=0.569).

6 DISCUSSION

6.1 MANAGEMENT OF ACUTE HEART FAILURE ACCORDING TO CLINICAL PRESENTATION

6.1.1 UTILIZATION OF DIURETICS

This study confirms the findings of various other studies that diuretics, most often furosemide, are the primary choice of clinicians in initial AHF management as recommended by the guidelines (I).[28,95,96] IV furosemide use seems frequent regardless of clinical presentation, clinical class, or initial SBP. Although variation has occurred, most studies have reported that of every 10 AHF patients, 8 to 9 received furosemide.[4,7,11,14,15,36,97,98] Similar observations from the Middle East and Europe have appeared more recently, thus further consolidating the role of diuretics in real-life AHF management.[5,6,53] The somewhat small discrepancies in numbers among studies may be explained by differences in local practices and in preferences of clinicians with regard to administration route of the drug, as some analyses, including ours, have omitted oral dosing.

Furosemide is frequent in the acute phase for CS patients, as well (I, III). In the FINN-AKVA study population, a majority and almost three-quarters of patients had already received furosemide already within the first 12 h after admission (I). Of the CS patients in the CardShock study population, 61% were treated with IV furosemide within the first 24 hours; the median cumulative dose rose as high as 120 (40-215 mg) (III). Considering that many CS patients experience at least relative hypovolemia and most have a need for potent vasopressor therapy, the rationale for using diuretics in the initial phase can be questioned. Although fluid accumulation is associated with increased mortality both in CS[143] and the critically ill overall, causality between the two and the benefit of de-resuscitation or diuretic use on mortality are yet to be proven.[142,232,233] Furthermore, diuretic use was independently associated with increased incidence of AKI (IV). It seems that diuretics in AHF are the mainstay in relieving congestion and symptoms of dyspnea, despite their unproven effect on patient outcome or mortality and, moreover, regardless of the patients' clinical profile.

6.1.2 OPIOIDS AND VENTILATORY SUPPORT

Use of opioids was rather frequent (for 29% of all AHF patients) and especially in PE (54%) (I). Frequent use has been reported by the EHFS II study and an analysis from the ADHERE registry (19% in both).[7,123] More recently, two studies specifically on morphine use in AHF overall have

reported lower rates (6-9%).[124,234] Opioid, or morphine, use has been more frequent in PE[7] (for up to 51% of patients in the 3CPO trial studying NIV in PE)[122]. Indeed, morphine has been recommended in the ESC guidelines, although currently only cautiously.[28] Concerns for the safety of morphine use have arisen in retrospective analyses but it is possible that morphine has been given to the sickest and most dyspneic patients.[235] Still, the data on a strong association with increased mortality from the ADHERE registry[123] and most recently from a propensity score-matched analysis is worrisome.[124] Benzodiazepines have been suggested as an alternative in PE,[235] and the randomized MIMO trial will hopefully provide information as to whether they or morphine should be the choice.[236]

Evidence suggests that regional variation in use of ventilatory support and utilization of NIV has ranged from 1% to 10%.[4,5,7,11] Although only half of PE patients were treated with NIV, its utilization was still significantly more common than in comparable studies.[7,9] NIV has been recommended in the Finnish guidelines for years, and indeed it has been demonstrated to relieve symptoms and reduce the need for intubation, and perhaps even reduce mortality.[127,237,238] The guidelines have had no specific recommendation concerning NIV or invasive mechanical ventilation in CS. Many studies have reported a much lower utilization rate of NIV, and intubation seems to be preferred.[19,22,239] Then again, the rationale for NIV is its alleviation of symptoms and reduction in the work of breathing, and its beneficial effects on hemodynamics,[127] likely via positive expiratory end pressure.[126] Actually, a recent analysis from the CardShock study population suggested that NIV is a safe option in selected CS patients.[240]

6.1.3 SBP AND MANAGEMENT

As clinical classification is not always straightforward and requires interpretation, Study I included admission SBP, which strongly correlates with clinical presentation overall and with other classifications. Correlation of SBP with nitrate use turned out to be positive, especially in PE and awCHF, while being inverse with vasopressors and inotropes. Furthermore, in adjusted analyses the associations remained independent and significant. No such association appeared for use of furosemide. Previous data on the effect of SBP on utilization of AHF therapies has been scarce, but an analysis of PE patients from the ALARM-HF survey showed similar results.[9] The association between SBP and use of these therapies seems logical, and SBP is indeed a guiding factor in the current ESC guidelines for vasoactive medications.[28]

An inverse association between SBP and mortality has been well acknowledged in the past and recognized in more recent studies as well.[241] Its effect on short-term mortality has been rather clear, and the FINN-AKVA study showed the association to remain over the long-term as well;[225] this finding was, however, challenged by a recent European multicenter analysis

showing that SBP had no impact on post-discharge mortality.[6] Nevertheless, considering that patients with lower SBP have poorer prognosis at least in the short-term, they should be treated according to AHF guidelines; those not truly hypotensive should receive nitrates and diuretics, for example, instead of inotropes and vasopressors.

6.1.4 UTILIZATION OF NITRATES

Whereas nitrate utilization was somewhat similar to that in other European studies, variation has, however, been greater than in use of diuretics. IV nitrates seem to be less frequently used in North America than other regions,[97] which may in part be due to a preference for non-IV administration[98] or to use of nesiritide instead of nitrates.[8] In addition, when comparing studies originating from the same region, there may be a trend toward diminished nitrate administration over time; in two Italian AHF studies the frequency of nitrate use decreased from 51% in 2004 to 30% during 2007-2009,[4,36] and in two multinational European studies from 38% in 2004-2005 to 19% in 2009-2010.[7,14] The ESC guidelines of 2005 and 2008 still had a class I recommendation for IV nitrates, alongside or as even being preferred over diuretics to be the main symptom-relieving therapy,[44,45] but the class of recommendation was lowered in the 2012 guidelines, probably due to lack of robust evidence on their relieving dyspnea or improving outcome.[28,31] This temporal association may reflect an overall change in local preferences for AHF medication or vasodilator therapy in Europe.

Whereas frequent use of nitrates in PE is logical, their utilization in hypertensive HF was rather infrequent, with even lower rates (down to 33%) reported.[6,7,15] Of note, nitrate use in PE seems to have decreased, as well: a recent report from the ESC-HF-LT observed utilization in only 46% of PE patients.[6] Such low utilization seems confusing regarding the recommendations in both earlier *and* current guidelines.[28,31,44,45] In line with this observation, a study from the UK reported that only 12% of patients admitted to hospital due to AHF and fulfilling the ESC guidelines criteria for IV nitrate use actually received the drug.[242] Reasons for the low rates and reluctance to use nitrates may include fear of hypotension, belief in or observance of a sufficient effect from diuretics, or lack of evidence for nitrates' beneficial effects on outcome.

The most recent Cochrane review found no evidence favoring nitrates in AHF; the four studies included were, however, of low quality.[113]. A more recent review of emergency department patients with AHF suggested that nitrates are safe and may even have beneficial short-term effects, particularly when used in high bolus doses.[243] High-dose nitrates, and nitrates in intermittent boluses instead of continuous infusion, may reduce the need for mechanical ventilation,[164,244,245] reduce MIs in severe PE,[244] reduce the need for intensive care[164,245,246] and shorten length of hospital stay.[246] One of the trials, which was randomized, showed that high-dose boluses of isosorbide

dinitrate combined with low-dose furosemide was more effective than was low-dose isosorbide dinitrate with high-dose furosemide in terms of need for mechanical ventilation and in terms of occurrence of MI, and had fewer adverse effects.[244]

Importantly, all these studies have reported the incidence and clinical relevance of hypotension to be very small or even non-existent. Some data suggest a beneficial effect for vasodilators in advanced low-output HF and particularly in patients with low SBP.[226,247] Explanations may include an increase in CO due to a reduction in LV afterload via arteriodilation, and an increase in venous capacitance and a reduction in congestion due to venodilation. Most of the data above are, however, derived from non-randomized studies.

Although current evidence of a beneficial effect on outcome is very limited, it seems that vasodilators, and especially nitrates, are safe, with few adverse effects. As they are the main AHF pharmacotherapy, along with diuretics, and are available and recommended by both European and US guidelines,[28,95,96] higher utilization rates, especially in hypertensive AHF, would seem justifiable.

6.2 ACUTE HEART FAILURE WITH AND WITHOUT ACUTE CORONARY SYNDROME

6.2.1 PATIENT OUTCOME

This study shows that ACS-AHF is related to elevated short-term mortality, but survival after discharge without ACS was somewhat similar (II), as has been reported elsewhere.[4,10,70] Likewise, the EHFS II study reported no association between ACS and post-discharge mortality.[3] Similarly, the GREAT registry also has reported a risk for death seemingly high during the first week after admission and thereafter declining.[13]

A similar discrepancy between short- and long-term mortality has emerged from the two other studies specifically focusing on patients with and without concomitant ACS: in an Israeli study,[71] and more recently a study from the HEARTS registry.[12] One explanation for this may be a difference in proportion of chronic HF between ACS and non-ACS patients.[12] Patients with CHF are older and have more comorbidities.[61,224] In addition, as most ACS cases seem to have *de novo* AHF, their changes in loading conditions and cardiac function may be more abrupt and the consequences more deleterious than in more adapted chronic conditions. This may also be one of the reasons that AHF treatments, especially both nitrates *and* vasopressors and inotropes in non-CS patients with low to normal SBP, were the choice more often in *de novo* AHF than awCHF (I). It is also possible that successful treatment of

ACS and AHF evolves less often into long-term consequences such as chronic HF. Indeed, awCHF is associated with markedly poorer long-term survival than is *de novo* AHF.[61,225] Although ACS-related mortality difference in *de novo* AHF was of borderline significance, it is still worth noting that ACS patients had comparably poor prognosis than did nACS-AHF patients, who presented most often with awCHF.

Results are also conflicting regarding the independent effect of ACS on mortality. A substudy of the ALARM-HF survey found no independent association between ACS and in-hospital mortality,[9] but their study population included only patients with PE. Then, the recent ESC-HF-LT study, which had separated ACS-HF into its own clinical class in addition to the other five classes, reported an in-hospital mortality of ACS-AHF lower than the average;[6] the classification of AHF seems, however, somewhat different from this study's, because a considerable proportion of patients in non-ACS classes had, as their AHF precipitating factor, myocardial ischemia.

6.2.2 MANAGEMENT OF ACS IN AHF

The clinical importance of the increased short-term mortality in ACS cannot be overlooked, and every effort should go toward countering the high risk of death. Although guidelines have recommended coronary angiography in ACS-AHF,[28,31,44,45,95] and early angiography has been associated with increased utilization of appropriate cardiac medication, myocardial revascularization, and reduced mortality,[134] and early revascularization may improve outcomes,[248] utilization of invasive coronary procedures in AHF has been rather low.[4,7,15,135,136] Illogically, in ACS complicated by HF compared to ACS without HF, similar observations have emerged.[129-131,133] In line with earlier observations, only a minority of ACS-AHF patients had undergone coronary angiography or other procedures during their index hospitalization (II).

Low utilization of coronary angiography may be related to differences in local practices or in availability of coronary angiography at participating centers. However, coronary angiography was already a common method in Finland during the FINN-AKVA study enrollment,[249] and patients with troponin elevations were considered at high risk, with a 2002 ACS-guideline recommendation for coronary angiography "as soon as possible" and "at least within the hospitalization period."[250] Because of frequent troponin elevations in AHF irrespective of concomitant ACS,[40] differential diagnosis between ischemic and non-ischemic AHF by use of troponin measurements may prove difficult.[251] However, troponin elevation in AHF, regardless of ischemic etiology, is associated with worse outcomes.[40,157] On the other hand, patients with ACS frequently had a history of CAD; their coronary anatomy in some cases may have been already known and considered nonamenable to revascularization. Other explanations may include fear of contrast-induced AKI, overlap between ACS and AHF symptoms, and attenuation of ACS-

related symptoms due to comorbidities (e.g. diabetes) and concomitant medications (β blockers, calcium-channel blockers, nitrates). Regardless of this, higher utilization of coronary angiography and early revascularization may have been able to improve survival.

Of note, while the current ESC guidelines recommend pursuit of an immediate (<2 hours after admission) invasive strategy aiming for revascularization,[28,62] the previous guidelines had formulated less aggressive recommendations.[31,44,45] Actually, the HEARTS registry and the ESC-HF-LT have, since Study II, observed higher rates (45% in each) in ACS-AHF.[6,12] This was, however, in contrast with a recent report in which patients with worsening HF and ACS underwent angiography within 30 days at a rate of only 23%.[252] Although the rates may still be rather low with respect to guideline recommendations, the shift towards a more vigorous approach to investigating and treating ACS in AHF may soon translate into favorable patient outcomes.

6.2.3 MANAGEMENT OF AHF IN ACS-AHF

AHF treatment recommendations have been based on clinical features other than ACS, thus resulting in a one-size-fits-all approach. The recommended AHF therapies were, however, more often used in ACS-AHF, probably due to its worse clinical presentation. Apart from variations related to furosemide, reports have been similar.[12,71] Rapid reduction in ventricular filling pressures is warranted in AHF, especially in worse clinical presentations like PE, which was more common in ACS-AHF; however, furosemide with a diuretic effect may not always be the appropriate choice, because ACS most often appears as *de novo* AHF, resulting in acute ventricular failure rather than in fluid retention. Nitrates might prove preferable for this purpose in patients without shock or hypoperfusion, and they are also recommended for symptom relief in ACS.[62,63] Furthermore, the ESC guidelines recommend nitrates for STEMI patients with concomitant HF unless they are hypotensive,[63] making it logical that nitrates along with opioids were more often used in ACS-AHF (II). However, it is also possible that nitrates and opioids have been adopted for treatment of chest pain and ischemia rather than for dyspnea and congestion.

A very recent study from the GREAT registry reported that administration of β blockers and ACEis /ARBs at hospital discharge is associated with better survival in AHF.[253] Thus, it is encouraging that evidence-based oral therapies were described equally often in ACS-AHF and nACS-AHF (II) and recently even more frequently in ACS-AHF.[12] More common use of mineralocorticoid receptor antagonists /spironolactone in nACS-AHF in both studies is most likely explained by chronic HF.

All in all, physicians might well react to ACS differently from the way they react to AHF, and treat ACS more aggressively. It should be borne in mind, however, that AHF outcome is at least as poor as or worse than is ACS

outcome.[16,49,225,254,255]. The need is urgent to design trials taking into account the uniqueness of ACS-AHF in terms of both pathophysiology and treatment strategy. Indeed, what should be tested is whether the high short-term risk of death in ACS-AHF might be reduced by timely revascularization or optimal medical therapy, or both.

6.3 VASOPRESSORS AND INOTROPES IN ACUTE HEART FAILURE

6.3.1 AHF WITHOUT SHOCK

Vasopressors and inotropes are mainly recommended for patients in shock, i.e. with significant hypotension or organ hypoperfusion, or both.[28] Nonetheless, they are used rather frequently in AHF patients without cardiogenic shock or even in hypertensive patients.[4-9,11,15,36,53,151,154] This study produced similar observations, although their utilization was somewhat less frequent than in other studies (I). However, comparing overall use of these therapies is not straightforward, because distributions of clinical presentations or classes differ among study populations. In addition, some studies may have had specific inclusion criteria such as a need for IV medication or admission to cardiac or intensive care.[4] Still, patients with PE have been especially likely to receive vasoactive medications.[6,7,9]

This study shows that utilization of vasopressors and inotropes was relatively frequent in patients without CS, especially in PE and *de novo* AHF, and the initial SBP was not hypotensive but rather high among treated patients. Considering the recommendations [28,31,44,45] and the available data on possible harm to AHF patients, in particular to those without shock and hypoperfusion,[149-155] this study found possibly unwarranted use of these medications, especially vasopressors or inopressors. Similar findings or even higher utilization rates in higher SBP categories have been observable in the ALARM-HF.[9]

Vasopressor and inotrope use was especially frequent in ACS-AHF (II). While this may be explained by its more severe clinical presentation, the difference was rather striking considering the very small proportion of CS. Their seemingly liberal use is alarming, as these medications may be harmful for patients not in shock and particularly in those with ischemic heart disease or ACS.[68,69,150-152,157,256] Thus, efforts are essential—for example through education and training—to restrict them to patients with marked hypotension or hypoperfusion.

6.3.2 CARDIOGENIC SHOCK

This was a unique investigation focusing on real-life use of vasoactive medications in a contemporary cohort of CS patients (III). In addition to mortality, it analyzed the evolution of hemodynamic stabilization and organ injury in relation to use of selected treatment strategies. This study thus brings forth significant observations and safety concerns regarding vasoactive medications in CS.

Vasopressors, inotropes, or a combination are almost invariable in CS regardless of its etiology. In line with current recommendations,[28,63,78,79,141,148,179,257] noradrenaline is the most commonly administered vasopressor (75%). Similar utilization rates were reported from the IABP-SHOCK II trial and by a recent Korean study.[19,258] With regard to dopamine (administered to 26% of patients), much lower rates were reported from the IABP-SHOCK II trial[19] (4%), but significantly higher (up to 61%) rates by some other studies.[15,258] Variations in choice of specific vasoactives may reflect the paucity of randomized data on the superiority of one vasoactive medication over another,[180,259] and reflect variation in local practice also reported in AHF studies.[260,261]

Although dopamine is still in active use and included in some recommendations,[28,74] current knowledge does not support its use in shock. It is a weaker vasopressor than noradrenaline,[262] but, on the other hand, it seems that doses were low to intermediate, or "renal-inotropic,"[174] rather than aimed at high vasopressor effects. Evidence does not support use of even such "renal" doses[161,162] and overlap is substantial in dopamine's dose-dependent effects in the critically ill.[148] Additionally, when compared with noradrenaline, dopamine has more adverse effects such as arrhythmias,[263,264] and has been linked to increased mortality.[265] One multicenter trial randomized shock patients to either dopamine or noradrenaline as first-line therapy, and found, in a pre-defined subgroup analysis by shock type, 28-day mortality to be higher with dopamine than with noradrenaline among patients suffering CS.[264] Considering the available evidence, dopamine seems to have no indication in CS.[78,179]

6.3.2.1 Adrenaline and outcome

In the current guidelines, adrenaline is mostly restricted to resuscitation protocols. In hypotension refractory to other vasoactive medications, however, it is still considered an option.[28] Considering that it has more adverse effects and appears less safe than other vasoactive medications,[266,267] its use was unexpectedly frequent. Furthermore, in this study, most patients had not been resuscitated prior to receiving adrenaline. Of note, the administration rate in the IABP-SHOCK II trial was similar to that in Study III, but lower in the Korean study.[19,258]

Regardless of possible prior resuscitation from cardiac arrest, adrenaline is associated with marked aggravation of cardiac stress and injury and, more

importantly, with increased 90-day mortality. In part, more severe clinical presentation apparently led to treatment with adrenaline, but its association with poor prognosis remained despite rigorous statistical evaluation. Whereas adrenaline seems to improve hemodynamic parameters similarly to its vasopressor alternatives, it may produce intense adrenergic stimulation resulting in increased myocardial oxygen consumption and excessive vasoconstriction, and thus prove toxic to organs.

In short, because it seems that adrenaline may be associated with worsened outcomes and may even be harmful *per se*, alternative treatment strategies such as mechanical circulatory support should be considered instead of adrenaline for potent hemodynamic support. Studies and trials on optimal hemodynamic support are certainly long overdue.

6.3.2.2 Noradrenaline-inotrope combinations

Considering the results for adrenaline, alternative medical therapy seems preferable. A previous randomized trial including CS patients suggested that a noradrenaline-dobutamine combination could be safer than adrenaline alone, because the latter was associated with transient lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion.[267] Furthermore, an inodilator-inopressor combination has been associated with a more favorable outcome than use of an inopressor alone.[268] Indeed, in addition to correction of hypotension, organ hypoperfusion needs to be reversed promptly. Increasing blood pressure by vasopressors alone has not translated into beneficial patient outcome.[146] Vasopressors primarily increase blood pressure by vasoconstriction, which may, in excess, raise LV afterload and myocardial oxygen consumption and impair microcirculation. Instead, inodilators primarily elevate CO and, furthermore, produce vasodilation that may preserve the microcirculation[269] and organ perfusion, and thus improve patient outcomes. However, their use alone in shock is limited due to their vasodilatory effects, which was a likely reason why only 10% of patients received solely inotropes-/dilators.

A vasopressor-ino*dilator* combination would thus seem a preferable option. Noradrenaline is the preferred vasopressor, but comparative data on the choice of inodilator has been lacking. The paucity of scientific data on inotropes and their effect on mortality in AMI-CS was highlighted by a recent Cochrane review.[180] The present study provides valuable insight into this, as it compares the two most common inopressor-inodilator combinations: noradrenaline-dobutamine and noradrenaline-levosimendan. Although the latter seemed to associate with lower mortality in unadjusted analyses, the two combinations appeared to be equally safe and useful alternatives in adjusted analyses with respect to hemodynamic stabilization, organ injury, and mortality. Thus, these combinations might be preferred in CS; further studies are vital, however.

6.4 ACUTE KIDNEY INJURY IN CARDIOGENIC SHOCK

6.4.1 CREATININE-DEFINED AKI

Despite the frequency of and interest in AKI in AHF and in those critically ill, no contemporary and comprehensive data has covered these subjects in CS, making this study the first to describe AKI in CS by means of the KDIGO definitions (IV). Especially data on UO and CysC provide important new knowledge. Furthermore, hemodynamic alterations associated with AKI and UO are described here for the first time in CS.

In line with studies including unselected populations of critically ill patients, Study IV shows AKI to have been very frequent in CS, as well. Taking into account both creatinine and UO criteria of the KDIGO, most patients actually had already developed AKI during the first 24 hours after baseline. A substantial discordance existed between the two criteria, however. Strikingly, the UO criteria were far more frequently already fulfilled within the first 24 hours than was AKI_{crea} within the first 48 hours, and stage 2 AKI in particular was much more common according to the UO criterion than to the creatinine criterion. Indeed, the UO criteria have been suggested to be more sensitive for AKI detection than are creatinine criteria.[27,203] Of the predictors of $AKI_{crea,}$ diuretic use has been an AKI predictor overall in AHF[202] and in the critically ill,[25] and low arterial pH is an AKI predictor in ICU patients.[218] It is worth noting, however, that baseline renal function predicted independently only AKI_{UO}.

In CS, there are, to the author's knowledge, few studies providing insight into the subject of AKI specifically in CS. They have mainly focused on AMI-CS,[212-215,270] and one analyzed only AKI treated with renal replacement therapy.[214] In addition, criteria for AKI and patient populations have been rather heterogenous. Only one recent study used AKI-severity staging, but that study included modified KDIGO creatinine criteria and lacked any UO data. It reported only stage 3 AKI as predicting poor prognosis, but it comprised solely refractory CS treated with mechanical circulatory support.[216] Despite the discrepancies between the aforementioned studies, this study confirms two key messages: AKI is frequent in CS, and creatinine-based AKI, in particular, is associated with notably poor prognosis. The same is true with regard to studies on AKI that use the KDIGO criteria in unselected critically ill populations. What must be emphasized, however, is that mortality in CS is consistently higher, and mortality rates are still further increased by AKI_{crea}.

6.4.2 URINE OUTPUT IN AKI AND MORTALITY PREDICTION

Studies on critically ill and surgical patients have found UO to enhance sensitivity for AKI detection, and found AKI_{UO} to be more frequent than AKI_{crea}.[27,203,271,272] This study (IV) seems to confirm these observations in CS.

However, the concordance between AKI_{UO} and AKI_{crea} has been rather variable. While the FINNAKI study including Finnish ICU patients showed oliguria be to highly predictive of AKI_{crea},[273] many patients with oliguria in a US study did not subsequently develop AKI_{crea}.[274] Observations from the present study are even more conflicting, as a rather large proportion of patients with AKI_{UO} did not develop AKI_{crea} and vice versa. Consequently, the current UO threshold in the KDIGO guidelines had only a modest association with development of AKI_{crea}.

Data on AKI_{UO} in mortality prediction have been conflicting as well. Some studies have reported AKI_{UO} to be independently associated with increased mortality,[273] that patients with both AKI_{crea} and AKI_{UO} suffer the highest mortality,[27] or that UO has even outperformed creatinine in mortality prediction.[275] Conflicting reports also exist.[276,277] Results from this study fall into the latter category: AKI_{UO} overall did not associate with increased mortality. However, stage 2 AKI_{UO}, i.e. at least two consecutive 6-hour periods of average hourly UO of <0.5 ml/kg, was a significant predictor of increased mortality.

The current 6-hour UO definition for AKI_{UO} has been questioned in outcome prediction in one study that suggested a stricter cutoff of <0.3 ml/kg/h for 6 hours to be optimal for mortality prediction.[204] This stricter cutoff performed considerably better in 90-day mortality prediction in this study, as well. Combining it with AKI_{crea} seems to stratify patients well by mortality risk.

Some of the differences between studies mentioned above may be explained by the different ways to define the UO collection period. The FINNAKI substudy, for example, defined the duration as consecutive hours of UO below the study threshold,[273] while the other study, proposing the stricter UO cutoff, as also done in Study IV, averaged the UO within a 6-hour time interval.[204] While the former definition as the strictest interpretation of the AKI_{UO} criteria provides increased specificity, UO measured in fixed intervals provides increased sensitivity and has had the best positive predictive value for AKI.[203] Additionally, using fixed intervals is more practical and facilitates application of the criteria.

Although limitations apparently exist in use of UO in AKI definitions and outcome prediction, it is non-costly, easily measurable, and available for practically all critically ill patients. Thus, further studies on optimal use of UO in AKI detection and mortality prediction in CS seem reasonable.

6.4.3 HEMODYNAMIC DERANGEMENTS IN AKI

In addition to being a significant predictor of mortality, AKI is associated with significant hemodynamic alterations as well; no data in this context has, to the author's knowledge, appeared. Not only was persistent venous congestion—reflected by CVP increase—but also hypotension and

hypoperfusion—reflected by reduction in MAP and CI—were here associated with both AKI incidence and severity.

The role of venous congestion has been highlighted in development of WRF in cardiovascular diseases.[220-222] Whereas CO has played a role in WRF in a variety of cardiac settings, two studies have reported the role of CI in AHF to be limited at best.[222,278] Situtations such as hypoperfusion from a severe derangement in CO and low arterial pressure exceeding the autoregulation capacity of the kidney can each play a more relevant role in CS than in less severe forms of AHF. The backward failure and severe neurohormonal activation resulting from CS can result in a significant increase in venous congestion as well; venous congestion is further aggravated by fluid administered to counter hypotension and hypoperfusion. In addition to these hemodynamic derangements, the pronounced inflammatory response and neurohormonal activation further exacerbate renal injury and dysfunction. Furthermore, use of nephrotoxic agents such as contrast media and diuretics, may, under such markedly labile conditions produce excessively deleterious effects.

In addition to AKI_{crea}, AKI_{UO} was also associated with such hemodynamic alterations as these. However, the effect was more pronounced in, or seemingly more strongly driven by, a more significant reduction in UO than defined by the current UO cutoff for AKI. This is a further argument in favor of a stricter cutoff in CS.

6.4.4 CYSTATIN C AS A MARKER OF AKI

Cystatin C has been of value in AKI, and in mortality detection in the critically ill, and in AHF.[206-209,211] AKI_{CysC} now appears useful in mortality prediction in CS as well. Although one retrospective multicenter study showed AKI_{CysC} to be more predictive of short-term outcomes than AKI definitions by conventional markers in the critically ill, in the present study AKI_{CysC} provided no clear advantage over AKI_{crea}. However, similarly to a finding from the FINN-AKVA study concerning AHF patients overall,[210] in Study IV, CysC- and creatinine-based AKI definitions identified slightly different patient populations with differences in AKI stages. Indeed, the cutoff of a <0.3 mg/L increase has been accepted,[118,209,210,279] but staging of AKI_{CysC} needs further study.

CysC has been able to predict AKI at earlier time-points than does creatinine.[211] Here, albeit the difference was small, AKI_{CysC} was already detectable within the first 24 hours more frequently than was AKI_{crea}. CysC, at least as accurate as or even superior to creatinine in estimation of acute changes in eGFR,[206] is independent of height, gender, age, muscle mass and diet, giving it an advantage. The CysC-based AKI definition may prove particularly useful in the elderly and in patients with changes in muscle metabolism or mass due to such issues as catabolic critical illness. CysC

seems a feasible alternative as an AKI marker, but further studies are warranted and AKI staging according to CysC calls for validation.

6.5 LIMITATIONS

Some limitations must be acknowledged in this study. First, the FINN-AKVA study data were collected back in 2004. The pharmacotherapies available and other AHF treatments have, however, actually changed little over the years. Similarly, the ESC guidelines have remained practically the same, apart from a few adjustments, since the first ones in 2005. Thus, the findings of this study need not be considered outdated. Of note, similar discrepancies between utilization of pharmacotherapies and clinical profiles have been recently reported, despite updates to guidelines.

Second, because this study is observational, its findings on treatment effect are hypothesis-generating (III). The rigorous statistical evaluation by propensity score methods—serving to minimize any bias due to lack of randomization and due to confounding by indication—is, however, an asset. Although the estimates of treatment effect may be susceptible to bias due to unknown or unmeasured confounding, the association, for example, between adrenaline and poor outcome remained consistent throughout multiple analyses.

Third, although overall numbers of AHF and CS patients were reasonable, numbers in certain subgroups were limited. For example, numbers of patients in certain clinical classes such as hypertensive and right HF (I), and in treatment groups compared (III) were limited, thus requiring caution in interpretation of these results.

Fourth, treatment utilization until 12 to 48 hours from hospital admission was analyzed in relation to patient's initial presentation, but changes in clinical presentation after admission, such as in SBP, went unaccounted for (I-II). However, guidelines for the most acute-phase medications, i.e. furosemide and nitrates, are based on initial presentation, so these analyses were reasonable. Vasopressors and inotropes, which are not the first-line medications (CS excluded), were mostly initiated within the first 24 hours and the number of actual CS cases, corresponding to the rates in the AHF literature, was low when compared with these drugs' more prevalent use.

Fifth, no centralized adjudication in diagnoses occurred. However, diagnoses based on the clinical judgement of experienced local investigators reflect clinical practice.

6.6 CLINICAL IMPLICATIONS

The major strength of this study is that its data are based on prospective studies including patients with AHF and CS of various etiologies. Especially the CardShock study should be considered unique as well as contemporary, providing invaluable material and findings.

This study provides much fuel for serious thoughts for both clinicians and investigators. The study raises questions as to how well the guidelines and recommended therapies are implemented in clinical practice currently (I-III). The findings may indicate a need to review guideline implementation individually, locally, or on a wider scale.

Available AHF therapies have remained practically the same for years, but discrepancies still exist between therapy utilization and guideline recommendations for different clinical profiles. In addition, knowledge is increasing on the potential harms rather than the benefits of particular pharmacotherapies. This study points out, for example, the liberal use of inotropes and vasopressors that should be avoided in patients without shock; other treatments should be the choice instead. This study enhances awareness of heterogenous clinical manifestations and draws attention to optimizing AHF management according to clinical profile. This offers the possibility of improving adherence to guidelines.

With regard to specific vasoactives, adrenaline strongly associated with poor outcome (III). While the observational nature of the study advocates for caution in interpretation of results, the safety concerns are rather serious, and other treatment options should be considered in refractory CS. Indeed, randomized studies on optimal hemodynamic support are warranted.

The study on ACS-AHF (II) describes the special features of this entity and the low use of angiography and revascularization, and corroborates a previous observation on elevated short-term mortality risk in those patients. Thus, it seems reasonable to put all effort possible into optimizing invasive coronary procedures. The focus should be on the clinical entity, both in clinical practice and in future trials, and the effect of early revascularization should be tested.

Knowledge of the frequency and prognostic importance of AKI in CS raises awareness and can help clinicians detect AKI with easily available and inexpensive biomarkers. Moreover, this issue reminds us to avoid AKI-provoking procedures in selected cases and should promote in prognosis assessment (IV). As this particular entity and accompanying hemodynamic alterations are described here for the first time, this study serves also as a platform for further studies on, for example, optimal AKI detection and its underlying, potentially avoidable, mechanisms.

7 CONCLUSION

Initial management of AHF includes utilization of IV medications and ventilatory support. Furosemide is the drug of choice for most cases, and a clear majority of patients, regardless of clinical presentation, already receive it in the initial phase (I), even in CS (IV). Not only does use of other therapies vary, but prognosis also varies based on the clinical profile of AHF (I-II).

Strongly predictive of patient outcome in AHF is SBP on admission (I). SBP was also one of the main factors related to utilization of AHF therapies. In part, interconnected with SBP but describing the severity and clinical picture better than does any single parameter, is clinical classification, which was similarly associated with AHF management.

Nitrates, currently the main vasodilators, were utilized less frequently than expected, when considering the guideline recommendations (I). While their use has a strong positive association with SBP, hypotension does not fully explain their low frequency, and hypertensive AHF patients, for example, strikingly seldom received nitrates.

ACS-AHF is an important clinical entity often presenting as *de novo* AHF and with a more severe clinical picture than nACS-AHF (II). Intravenous therapies and invasive coronary procedures are more frequent in ACS-AHF; angiography and revascularization rates have, however, been rather low with respect to guideline recommendations. Short-term outcome is poorer in ACS-AHF, and, indeed, an urgent need exists to design AHF trials taking into account the unique nature of ACS-AHF.

Vasopressors and inotropes play an important role in hemodynamic stabilization but are mainly restricted to patients in shock. Still, their use was alarmingly liberal in patients without shock, especially in those with ACS (I-II). In CS, they were used almost invariably; noradrenaline was the current vasopressor of choice, and dobutamine the most common inotrope (III). Adrenaline was associated with pronounced cardiac injury and excess mortality, raising safety concerns about its utility. Noradrenaline with either dobutamine or levosimendan seems a safer alternative; the two combinations appeared prognostically equal. Nevertheless, the benefit of alternative strategies should be promptly and properly investigated.

AKI is already frequent during the first 48 hours of CS and is associated with poor prognosis (IV). Not only are the KDIGO AKI criteria of creatinine and UO in conflict, staging by creatinine and UO are also in conflict with each other. Whereas AKI_{crea} was a strong predictor of a particularly poor outcome and is thus useful in prognosis determination, the AKI_{UO} definition seems rather liberal and was not independently associated with increased mortality. A stricter 6-hour UO cutoff of <0.3 ml/kg/h improved mortality prediction in CS. CysC seems a plausible alternative to creatinine in defining AKI and in outcome evaluation.

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